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(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

11729.1 contg

11729-45.21.21.cons1

11729-45.21.21.cons2

11731.1cont1g

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as ovarian cancer, are disclosed. Compositions may comprise one or more ovarian carcinoma proteins, immunogenic portions thereof, polynucleotides that encode such portions or antibodies or immune system cells specific for such proteins. Such compositions may be used, for example, for the prevention and treatment of diseases such as ovarian cancer. Methods are further provided for identifying tumor antigens that are secreted from ovarian carcinomas and/or other tumors. Polypeptides and polynucleotides as provided herein may further be used

for the diagnosis and monitoring of ovarian cancer.

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COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

Technical Field

The present invention relates generally to ovarian cancer therapy. The invention is more specifically related to polypeptides comprising at least a portion of an ovarian carcinoma protein, and to polynucleotides encoding such polypeptides, as well as antibodies and immune system cells that specifically recognize such polypeptides. Such polypeptides, polynucleotides, antibodies and cells may be used in vaccines and pharmaceutical compositions for treatment of ovarian cancer.

10 Background of the Invention

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Ovarian cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and therapy of this cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Management of the disease currently relies on a combination of early diagnosis and aggressive treatment, which may include one or more of a variety of treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. However, the use of established markers often leads to a result that is difficult to interpret, and high mortality continues to be observed in many cancer patients.

Immunotherapies have the potential to substantially improve cancer treatment and survival. Such therapies may involve the generation or enhancement of an immune response to an ovarian carcinoma antigen. However, to date, relatively few ovarian carcinoma antigens are known and the generation of an immune response against such antigens has not been shown to be therapeutically beneficial.

Accordingly, there is a need in the art for improved methods for identifying ovarian tumor antigens and for using such antigens in the therapy of ovarian cancer. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

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Briefly stated, this invention provides compositions and methods for the therapy of cancer, such as ovarian cancer. In one aspect, the present invention provides polypeptides comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished. Within certain embodiments, the ovarian carcinoma protein comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:456-457, 460-477 and 512-570 and complements of such polynucleotides.

The present invention further provides polynucleotides that encode a polypeptide as described above or a portion thereof, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences recited in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596.

Within other aspects, the present invention provides pharmaceutical compositions and vaccines. Pharmaceutical compositions may comprise a physiologically acceptable carrier or excipient in combination with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma proteinspecific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570 or (ii) a polynucleotide encoding such a polypeptide; (iii) an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide. Vaccines may comprise a non-specific immune response enhancer in combination with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions

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and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence set forth in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596 or an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570 or (ii) a polynucleotide encoding such a polypeptide; (iii) an anti-idiotypic antibody that is specifically bound by an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

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Within related aspects, pharmaceutical compositions comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for stimulating and/or expanding T cells, comprising contacting T cells with (a) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence set forth in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596 or an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570; (b) a polynucleotide encoding such a polypeptide and/or (c) an antigen presenting cell that

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expresses such a polypeptide under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Such polypeptide, polynucleotide and/or antigen presenting cell(s) may be present within a pharmaceutical composition or vaccine, for use in stimulating and/or expanding T cells in a mammal.

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Within other aspects, the present invention provides methods for inhibiting the development of ovarian cancer in a patient, comprising administering to a patient T cells prepared as described above.

Within further aspects, the present invention provides methods for inhibiting the development of ovarian cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570; (ii) a polynucleotide encoding such a polypeptide; or (iii) an antigen-presenting cell that expresses such a polypeptide; such that T cells proliferate; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of ovarian cancer in the patient. The proliferated cells may be cloned prior to administration to the patient.

The present invention also provides, within other aspects, methods for identifying secreted tumor antigens. Such methods comprise the steps of: (a) implanting tumor cells in an immunodeficient mammal; (b) obtaining serum from the immunodeficient mammal after a time sufficient to permit secretion of tumor antigens into the serum; (c) immunizing an immunocompetent mammal with the serum; (d) obtaining antiserum from the immunocompetent mammal; and (e) screening a tumor expression library with the antiserum, and therefrom identifying a secreted tumor antigen. A preferred method for identifying a secreted ovarian carcinoma antigen comprises the steps of: (a) implanting ovarian carcinoma cells in a SCID mouse; (b) obtaining serum from the SCID mouse after a time sufficient to permit secretion of

ovarian carcinoma antigens into the serum; (c) immunizing an immunocompetent mouse with the serum; (d) obtaining antiserum from the immunocompetent mouse; and (e) screening an ovarian carcinoma expression library with the antiserum, and therefrom identifying a secreted ovarian carcinoma antigen.

The present invention also discloses antibody epitopes recognized by the O8E polyclonal anti-sera which epitopes are presented herein as SEQ ID NO: 394-415.

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Further disclosed by the present invention are 10-mer and 9-mer peptides predicted to bind HLA-0201 which peptides are disclosed herein as SEQ ID NO:416-435 and SEQ ID NO:436-455, respectively.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

In another aspect of the present invention, the applicants have unexpectedly identified a series of novel repeating sequence elements in the 5' end of the gene encoding O772P. Therefore, the present invention provides O772P polypeptides having structures represented by X_n -Y, wherein X comprises a sequence having at least 50% identity, preferably at least 70% identity, and more preferably at least 90% identity with an O772P repeat sequence set forth in SEQ ID NO: 596. Y will typically comprise a sequence having at least 80% identity, preferably at least 90% identity and more preferably at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 594. According to this embodiment, n will generally be an integer from 1 to 35, preferably an integer from 15 to 25, and X can be the same or different.

In one preferred embodiment, X comprises a sequence selected from the group consisting of any one of SEQ ID NOs: 574-593 and Y comprises the sequence set forth in SEQ ID NO: 594.

In another preferred embodiment, an illustrative O772P polypeptide comprises the sequence set forth in SEQ ID NO: 595, containing 20 repeating sequence elements (i.e., X_{20}) wherein the X elements are arranged in the following order (moving from N-terminal to C-terminal in the O772P repeat region): SEQ ID NO: 574 - SEQ ID

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NO: 575 - SEQ ID NO: 576 - SEQ ID NO: 577 - SEQ ID NO: 578 - SEQ ID NO: 579 - SEQ ID NO: 580 - SEQ ID NO: 581 - SEQ ID NO: 582 - SEQ ID NO: 583 - SEQ ID NO: 584 - SEQ ID NO: 585 - SEQ ID NO: 586 - SEQ ID NO: 587 - SEQ ID NO: 588 - SEQ ID NO: 589 - SEQ ID NO: 590 - SEQ ID NO: 591 - SEQ ID NO: 592 - SEQ ID NO: 593.

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According to another aspect of the present invention, an O772P polynucleotide is provided having the structure X_n -Y, wherein X comprises an O772P repeat sequence element selected from the group consisting of any one of SEQ ID NOs: 512-540, 542-546 and 548-567. Y will generally comprise a sequence having at least 80% identity, preferably at least 90% identity, and more preferably at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 568. In this embodiment, n is typically an integer from 1 to 35, preferably from 15 to 25 and X can be the same or different.

In another embodiment, an illustrative O772P polynucleotide comprises the sequence set forth in SEQ ID NO: 569, containing 20 repeating sequence elements (i.e., X₂₀).

According to another aspect of the present invention, O772 polypeptides are provided comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 490-511.

According to another aspect of the present invention, O8E polypeptides are provided comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 394-415.

BRIEF DESCRIPTION OF THE SEQUENCE IDENTIFIERS AND DRAWINGS

SEQ ID NO:1-71 are ovarian carcinoma antigen polynucleotides shown 25 in Figures 1A-1S.

SEQ ID NO:72-74 are ovarian carcinoma antigen polynucleotides shown in Figures 2A-2C.

SEQ ID NO:75 is the ovarian carcinoma polynucleotide 3g (Figure 4).

SEQ ID NO:76 is the ovarian carcinoma polynucleotide 3f (Figure 5).

30 SEQ ID NO:77 is the ovarian carcinoma polynucleotide 6b (Figure 6).

SEQ ID NO:78 is the ovarian carcinoma polynucleotide 8e (Figure 7A).

SEQ ID NO:79 is the ovarian carcinoma polynucleotide 8h (Figure 7B).

SEQ ID NO:80 is the ovarian carcinoma polynucleotide 12e (Figure 8).

SEQ ID NO:81 is the ovarian carcinoma polynucleotide 12h (Figure 9).

SEQ ID NO:82-310 are ovarian carcinoma antigen polynucleotides shown in Figures 15A-15EEE.

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SEQ ID NO:311 is a full length sequence of ovarian carcinoma polynucleotide O772P.

SEQ ID NO:312 is the O772P amino acid sequence.

SEQ ID NO:313-384 are ovarian carcinoma antigen polynucleotides.

SEQ ID NO:385 represents the cDNA sequence of a form of the clone O772P, designated 21013.

SEQ ID NO:386 represents the cDNA sequence of a form of the clone O772P, designated 21003.

SEQ ID NO:387 represents the cDNA sequence of a form of the clone O772P, designated 21008.

SEQ ID NOs:388 is the amino acid sequence corresponding to SEQ ID NO:385.

SEQ ID NOs:389 is the amino acid sequence corresponding to SEQ ID NO:386.SEQ ID NOs:390 is the amino acid sequence corresponding to SEQ ID NO:387.

SEQ ID NO:391 is a full length sequence of ovarian carcinoma polynucleotide O8E.

SEQ ID NO:392-393 are protein sequences encoded by O8E.

SEQ ID NO:394-415 are peptide sequences corresponding to the OE8 antibody epitopes.

SEQ ID NO:416-435 are potential HLA-A2 10-mer binding peptides predicted using the full length open-reading frame from OE8.

SEQ ID NO:436-455 are potential HLA-A2 9-mer binding peptides 30 predicted using the full length open-reading frame from OE8.

SEQ ID NO:456 is a truncated nucleotide sequence of the full length Genbank sequence showing homology to O772P

SEQ ID NO:457 is the full length Genbank sequence showing significant homology to O772P

SEQ ID NO:458 is a protein encoding a truncated version of the full length Genbank sequence showing homology to O772P

SEQ ID NO:459 is the full length protein sequence from Genbank showing significant homology to the protein sequence for O772P

SEQ ID NO:460 encodes a unique N-terminal portion of O772P contained in residues 1-70.

SEQ ID NO:461 contains unique sequence and encodes residues 1-313 of SEQ ID NO: 456.

SEQ ID NO:462 is the hypothetical sequence for clone O772P.

SEQ ID NO:463 is the cDNA sequence for clone FLJ14303.

15 SEQ ID NO:464 is a partial cDNA sequence for clone O772P.

SEQ ID NO:465 is a partial cDNA sequence for clone O772P.

SEQ ID NO:466 is a partial cDNA sequence for clone O772P.

SEQ ID NO:467 is a partial cDNA sequence for clone O772P.

SEQ ID NO:468 is a partial cDNA sequence for clone O772P.

SEQ ID NO:469 is a partial cDNA sequence for clone O772P.

SEQ ID NO:470 is a partial cDNA sequence for clone O772P.

SEQ ID NO:471 is a partial cDNA sequence for clone O772P.

SEQ ID NO:472 is a partial cDNA sequence for clone O772P.

SEQ ID NO:473 is a partial cDNA sequence for clone O772P.

SEQ ID NO:474 is a partial cDNA sequence for clone O772P.

SEQ ID NO:475 is a partial cDNA sequence for clone O772P.

SEQ ID NO:476 is a partial cDNA sequence for clone O772P.

SEQ ID NO:477 represents the novel 5'-end of the ovarian tumor antigen

O772P.

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30 SEQ ID NO:478 is the amino acid sequence encoded by SEQ ID NO:462.

SEQ ID NO:479 is the amino acid sequence encoded by SEQ ID NO:463.

SEQ ID NO:480 is a partial amino acid sequence encoded by SEQ ID NO:472.

5 SEQ ID NO:481 is a partial amino acid sequence encoded by a possible open reading frame of SEQ ID NO:471.

SEQ ID NO:482 is a partial amino acid sequence encoded by a second possible open reading frame of SEQ ID NO:471.

SEQ ID NO:483 is a partial amino acid sequence encoded by SEQ ID NO:467.

SEQ ID NO:484 is a partial amino acid sequence encoded by a possible open reading frame of SEQ ID NO:466.

SEQ ID NO:485 is a partial amino acid sequence encoded by a second possible open reading frame of SEQ ID NO:466.

SEQ ID NO:486 is a partial amino acid sequence encoded by SEQ ID NO:465.

SEQ ID NO:487 is a partial amino acid sequence encoded by SEQ ID NO:464.

SEQ ID NO:488 represents the extracellular, transmembrane and 20 cytoplasmic regions of O772P.

SEQ ID NO:489 represents the predicted extracellular domain of O772P.

SEQ ID NO:490 represents the amino acid sequence of peptide #2 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:491 represents the amino acid sequence of peptide #6 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:492 represents the amino acid sequence of peptide #7 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:493 represents the amino acid sequence of peptide #8 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:494 represents the amino acid sequence of peptide #9 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:495 represents the amino acid sequence of peptide #11 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:496 represents the amino acid sequence of peptide #13 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:497 represents the amino acid sequence of peptide #22 which corresponds to an O772P specific antibody epitope.

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SEQ ID NO:498 represents the amino acid sequence of peptide #24 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:499 represents the amino acid sequence of peptide #27 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:500 represents the amino acid sequence of peptide #40 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:501 represents the amino acid sequence of peptide #41 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:502 represents the amino acid sequence of peptide #47 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:503 represents the amino acid sequence of peptide #50 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:504 represents the amino acid sequence of peptide #51 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:505 represents the amino acid sequence of peptide #52 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:506 represents the amino acid sequence of peptide #53 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:507 represents the amino acid sequence of peptide #58 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:508 represents the amino acid sequence of peptide #59 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:509 represents the amino acid sequence of peptide #60 which corresponds to an O772P specific antibody epitope.

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SEQ ID NO:510 represents the amino acid sequence of peptide #61 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:511 represents the amino acid sequence of peptide #71 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:512 (O772P repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:513 (O772P repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:514 (O772P repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:515 (O772P repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:516 (O772P repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:517 (HB repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:518 (HB repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:519 (HB repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:520 (HB repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:521 (HB repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:522 (HB repeat6 5'-end) represents an example of a cDNA sequence corresponding to repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:523 (1043400.1 repeat1) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:524 (1043400.1 repeat2) represents an example of a cDNA sequence corresponding to repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:525 (1043400.1 repeat3) represents an example of a cDNA sequence corresponding to repeat number 10/11 from the 5' variable region of O772P.

SEQ ID NO:526 (1043400.1 repeat4) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:527 (1043400.1 repeat5) represents an example of a cDNA sequence corresponding to repeat number 14 from the 5' variable region of O772P.

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SEQ ID NO:528 (1043400.1 repeat6) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:529 (1043400.3 repeat1) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:530 (1043400.3 repeat2) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:531 (1043400.5 repeat1) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P.

SEQ ID NO:532 (1043400.5 repeat2) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P, in addition containing intron sequence.

SEQ ID NO:533 (1043400.5 repeat2) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:534 (1043400.8 repeat1) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:535 (1043400.8 repeat2) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:536 (1043400.8 repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:537 (1043400.9 repeat1) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:538 (1043400.9 repeat2) represents an example of a cDNA sequence corresponding to repeat number 5 from the 5' variable region of O772P.

SEQ ID NO:539 (1043400.9 repeat3) represents an example of a cDNA sequence corresponding to repeat number 7 from the 5' variable region of O772P.

SEQ ID NO:540 (1043400.9 repeat4) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P.

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SEQ ID NO:541 (1043400.11 repeat1) represents an example of a cDNA sequence corresponding to repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:542 (1043400.11 repeat2) represents an example of a cDNA sequence corresponding to repeat number 2 from the 5' variable region of O772P.

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SEQ ID NO:543 (1043400.11 repeat3) represents an example of a cDNA sequence corresponding to repeat number 3 from the 5' variable region of O772P.

SEQ ID NO:544 (1043400.11 repeat4) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:545 (1043400.11 repeat5) represents an example of a cDNA sequence corresponding to repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:546 (1043400.12 repeat1) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:547 (PB repeatA) represents an example of a cDNA sequence corresponding to repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:548 (PB repeatB) represents an example of a cDNA sequence corresponding to repeat number 2 from the 5' variable region of O772P.

SEQ ID NO:549 (PB repeatE) represents an example of a cDNA sequence corresponding to repeat number 3 from the 5' variable region of O772P.

SEQ ID NO:550 (PB repeatG) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:551 (PB repeatC) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:552 (PB repeatH) represents an example of a cDNA sequence corresponding to repeat number 6 from the 5' variable region of O772P.

SEQ ID NO:553 (PB repeatJ) represents an example of a cDNA sequence corresponding to repeat number 7 from the 5' variable region of O772P.

SEQ ID NO:554 (PB repeatK) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P.

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SEQ ID NO:555 (PB repeatD) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:556 (PB repeatI) represents an example of a cDNA sequence corresponding to repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:557 (PB repeatM) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:558 (PB repeat9) represents an example of a cDNA sequence corresponding to repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:559 (PB repeat8.5) represents an example of a cDNA sequence corresponding to repeat number 13 from the 5' variable region of O772P.

SEQ ID NO:560 (PB repeat8) represents an example of a cDNA sequence corresponding to repeat number 14 from the 5' variable region of O772P.

SEQ ID NO:561 (PB repeat7) represents an example of a cDNA sequence corresponding to repeat number 15 from the 5' variable region of O772P.

SEQ ID NO:562 (PB repeat6) represents an example of a cDNA sequence corresponding to repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:563 (PB repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:564 (PB repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:565 (PB repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:566 (PB repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:567 (PB repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:568 represents the cDNA sequence form the 3' constant region.

SEQ ID NO:569 represents a cDNA sequence containing the consensus sequences of the 21 repeats, the 3' constant region and the 3' untranslated region.

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SEQ ID NO:570 represents the cDNA sequence of the consensus repeat sequence.

SEQ ID NO:571 represents the consensus amino acid sequence of one potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:572 represents the consensus amino acid sequence of a second potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:573 represents the consensus amino acid sequence of a third potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:574 represents the consensus amino acid sequence of repeat number 2 from the 5' variable region of O772P.

SEQ ID NO:575 represents the consensus amino acid sequence of repeat number 3 from the 5' variable region of O772P.

SEQ ID NO:576 represents the consensus amino acid sequence of repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:577 represents the consensus amino acid sequence of repeat number 5 from the 5' variable region of O772P.

SEQ ID NO:578 represents the consensus amino acid sequence of repeat number 6 from the 5' variable region of O772P.

SEQ ID NO:579 represents the consensus amino acid sequence of repeat number 7 from the 5' variable region of O772P.

SEQ ID NO:580 represents the consensus amino acid sequence of repeat number 8 from the 5' variable region of O772P.

SEQ ID NO:581 represents the consensus amino acid sequence of repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:582 represents the consensus amino acid sequence of repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:583 represents the consensus amino acid sequence of repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:584 represents the consensus amino acid sequence of repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:585 represents the consensus amino acid sequence of repeat number 13 from the 5' variable region of O772P.

SEQ ID NO:586 represents the consensus amino acid sequence of repeat number 14 from the 5' variable region of O772P.

5 SEQ ID NO:587 represents the consensus amino acid sequence of repeat number 15 from the 5' variable region of O772P.

SEQ ID NO:588 represents the consensus amino acid sequence of repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:589 represents the consensus amino acid sequence of repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:590 represents the consensus amino acid sequence of repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:591 represents the consensus amino acid sequence of repeat number 19 from the 5' variable region of O772P.

15 SEQ ID NO:592 represents the consensus amino acid sequence of repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:593 represents the consensus amino acid sequence of repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:594 represents the amino acid sequence of the 3' constant 20 region.

SEQ ID NO:595 represents an amino acid sequence containing the consensus sequences of the 21 repeats and the 3' constant region.

SEQ ID NO:596 represents the amino acid sequence of the consensus repeat sequence.

Figures 1A-1S (SEQ ID NO:1-71) depict partial sequences of polynucleotides encoding representative secreted ovarian carcinoma antigens.

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Figure 2A-2C depict full insert sequences for three of the clones of Figure 1. Figure 2A shows the sequence designated O7E (11731; SEQ ID NO:72), Figure 2B shows the sequence designated O9E (11785; SEQ ID NO:73) and Figure 2C shows the sequence designated O8E (13695; SEQ ID NO:74).

Figure 3 presents results of microarray expression analysis of the ovarian carcinoma sequence designated O8E.

Figure 4 presents a partial sequence of a polynucleotide (designated 3g; SEQ ID NO:75) encoding an ovarian carcinoma sequence that is a splice fusion between the human T-cell leukemia virus type I oncoprotein TAX and osteonectin.

Figure 5 presents the ovarian carcinoma polynucleotide designated 3f (SEQ ID NO:76).

Figure 6 presents the ovarian carcinoma polynucleotide designated 6b (SEQ ID NO:77).

Figures 7A and 7B present the ovarian carcinoma polynucleotides designated 8e (SEQ ID NO:78) and 8h (SEQ ID NO:79).

Figure 8 presents the ovarian carcinoma polynucleotide designated 12c (SEQ ID NO:80).

Figure 9 presents the ovarian carcinoma polynucleotide designated 12h (SEQ ID NO:81).

Figure 10 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 3f.

Figure 11 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 6b.

Figure 12 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 8e.

Figure 13 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 12c.

Figure 14 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 12h.

Figures 15A-15EEE depict partial sequences of additional polynucleotides encoding representative secreted ovarian carcinoma antigens (SEQ ID NO:82-310).

Figure 16 is a diagram illustrating the location of various partial O8E sequences within the full length sequence.

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Figure 17 is a graph illustrating the results of epitope mapping studies on O8E protein.

Figure 18 is graph of a fluorescence activated cell sorting (FACS) analysis of O8E cell surface expression.

Figure 19 is graph of a FACS analysis of O8E cell surface expression.

Figure 20 shows FACS analysis results for O8E transfected HEK293 cells demonstrating cell surface expression of O8E.

Figure 21 shows FACS analysis results for SKBR3 breast tumor cells demonstrating cell surface expression of O8E.

Figure 22 shows 08E expression in HEK 293 cells. The cells were probed with anti-08E rabbit polyclonal antisera #2333L.

Figure 23 shows the ELISA analysis of anti-08E rabbit sera.

Figure 24 shows the ELISA analysis of affinity purified rabbit anti-08E polyclonal antibody.

Figure 25 is a graph determining antibody internalization of anti-O8E mAb showing that mAbs against amino acids 61-80 induces ligand internalization.

DETAILED DESCRIPTION OF THE INVENTION

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As noted above, the present invention is generally directed to compositions and methods for the therapy of cancer, such as ovarian cancer. The compositions described herein may include immunogenic polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies that bind to a polypeptide, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells).

Polypeptides of the present invention generally comprise at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof. Certain ovarian carcinoma proteins have been identified using an immunoassay technique, and are referred to herein as ovarian carcinoma antigens. An "ovarian carcinoma antigen" is a protein that is expressed by ovarian tumor cells (preferably human cells) at a level that is at least two fold higher than the level in normal ovarian cells. Certain ovarian carcinoma antigens react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera generated against serum from an immunodeficient animal

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implanted with a human ovarian tumor. Such ovarian carcinoma antigens are shed or secreted from an ovarian tumor into the sera of the immunodeficient animal. Accordingly, certain ovarian carcinoma antigens provided herein are secreted antigens. Certain nucleic acid sequences of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence.

The present invention further provides ovarian carcinoma sequences that are identified using techniques to evaluate altered expression within an ovarian tumor. Such sequences may be polynucleotide or protein sequences. Ovarian carcinoma sequences are generally expressed in an ovarian tumor at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in normal ovarian tissue, as determined using a representative assay provided herein. Certain partial ovarian carcinoma polynucleotide sequences are presented herein. Proteins encoded by genes comprising such polynucleotide sequences (or complements thereof) are also considered ovarian carcinoma proteins.

Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to at least a portion of an ovarian carcinoma polypeptide as described herein. T cells that may be employed within the compositions provided herein are generally T cells (e.g., CD4⁺ and/or CD8⁺) that are specific for such a polypeptide. Certain methods described herein further employ antigen-presenting cells (such as dendritic cells or macrophages) that express an ovarian carcinoma polypeptide as provided herein.

Ovarian Carcinoma Polynucleotides

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Any polynucleotide that encodes an ovarian carcinoma protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides, and more preferably at least 45 consecutive nucleotides, that encode a portion of an ovarian carcinoma protein. More preferably, a polynucleotide encodes an immunogenic portion of an ovarian carcinoma protein, such as an ovarian carcinoma antigen. Polynucleotides complementary to any

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such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

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Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes an ovarian carcinoma protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native ovarian carcinoma protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native ovarian carcinoma protein or a portion thereof.

The percent identity for two polynucleotide or polypeptide sequences may be readily determined by comparing sequences using computer algorithms well known to those of ordinary skill in the art, such as Megalign, using default parameters. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, or 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Optimal alignment of sequences for comparison may be conducted, for example, using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. Preferably, the percentage of sequence identity is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the window may comprise additions or deletions (i.e., gaps) of 20 % or less, usually 5 to 15 %, or 10 to 12%, relative to the reference sequence (which does not contain additions or

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deletions). The percent identity may be calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e., the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native ovarian carcinoma protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

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It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, an ovarian carcinoma polynucleotide may be identified, as described in more detail below, by screening a late passage ovarian tumor expression library with antisera generated against sera of immunocompetent mice after injection of such mice with sera from SCID mice implanted with late passage ovarian tumors. Ovarian carcinoma polynucleotides may also be identified using any of a variety of techniques designed to evaluate differential gene expression. Alternatively, polynucleotides may

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be amplified from cDNA prepared from ovarian tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., an ovarian carcinoma cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with ³²P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target

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sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

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One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding portions of ovarian carcinoma antigens are provided in Figures 1A-1S (SEQ ID NO:1 to 71) and Figures 15A to 15EEE (SEQ ID NO:82 to 310). The sequences provided in Figures 1A-1S appear to be novel. For sequences in Figures 15A-15EEE, database searches revealed matches having substantial identity. These polynucleotides were isolated by serological screening of an ovarian tumor cDNA expression library, using a technique designed to identify secreted tumor antigens. Briefly, a late passage ovarian tumor expression library was prepared from a SCID-derived human ovarian tumor (OV9334) in the vector λ-screen (Novagen). The sera used for screening were obtained by

injecting immunocompetent mice with sera from SCID mice implanted with one late passage ovarian tumors. This technique permits the identification of cDNA molecules that encode immunogenic portions of secreted tumor antigens.

The polynucleotides recited herein, as well as full length polynucleotides comprising such sequences, other portions of such full length polynucleotides, and sequences complementary to all or a portion of such full length molecules, are specifically encompassed by the present invention. It will be apparent to those of ordinary skill in the art that this technique can also be applied to the identification of antigens that are secreted from other types of tumors.

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Other nucleic acid sequences of cDNA molecules encoding portions of ovarian carcinoma proteins are provided in Figures 4-9 (SEQ ID NO:75-81), as well as SEQ ID NO:313-384. These sequences were identified by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in an ovarian tumor than in normal ovarian tissue, as determined using a representative assay provided herein). Such screens were performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). SEQ ID NO:311 and 391 provide full length sequences incorporating certain of these nucleic acid sequences.

Any of a variety of well known techniques may be used to evaluate tumor-associated expression of a cDNA. For example, hybridization techniques using labeled polynucleotide probes may be employed. Alternatively, or in addition, amplification techniques such as real-time PCR may be used (see Gibson et al., Genome Research 6:995-1001, 1996; Heid et al., Genome Research 6:986-994, 1996). Real-time PCR is a technique that evaluates the level of PCR product accumulation during amplification. This technique permits quantitative evaluation of mRNA levels in multiple samples. Briefly, mRNA is extracted from tumor and normal tissue and cDNA is prepared using standard techniques. Real-time PCR may be performed, for example, using a Perkin Elmer/Applied Biosystems (Foster City, CA) 7700 Prism instrument. Matching primers and fluorescent probes may be designed for genes of interest using, for example, the primer express program provided by Perkin Elmer/Applied Biosystems

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(Foster City, CA). Optimal concentrations of primers and probes may be initially determined by those of ordinary skill in the art, and control (e.g., β-actin) primers and probes may be obtained commercially from, for example, Perkin Elmer/Applied Biosystems (Foster City, CA). To quantitate the amount of specific RNA in a sample, a standard curve is generated alongside using a plasmid containing the gene of interest. Standard curves may be generated using the Ct values determined in the real-time PCR, which are related to the initial cDNA concentration used in the assay. Standard dilutions ranging from 10-10⁶ copies of the gene of interest are generally sufficient. In addition, a standard curve is generated for the control sequence. This permits standardization of initial RNA content of a tissue sample to the amount of control for comparison purposes.

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Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding an ovarian carcinoma antigen, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo.

A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells or tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of an ovarian carcinoma protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches,

Futura Publishing Co. (Mt. Kisco, NY; 1994). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

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Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also

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be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

Ovarian Carcinoma Polypeptides

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Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof, as described herein. As noted above, certain ovarian carcinoma proteins are ovarian carcinoma antigens that are expressed by ovarian tumor cells and react detectably within an immunoassay (such as an ELISA) with antisera generated against serum from an immunodeficient animal implanted with an ovarian tumor. Other ovarian carcinoma proteins are encoded by ovarian carcinoma polynucleotides recited herein. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of an antigen that is recognized (i.e., specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of an ovarian carcinoma protein or a variant thereof. Preferred immunogenic portions are encoded by cDNA molecules isolated as described herein. Further immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with ovarian carcinoma protein-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "ovarian carcinoma protein-

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specific" if they specifically bind to an ovarian carcinoma protein (*i.e.*, they react with the ovarian carcinoma protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera, antibodies and T cells may be prepared as described herein, and using well known techniques. An immunogenic portion of a native ovarian carcinoma protein is a portion that reacts with such antisera, antibodies and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length protein. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A.

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As noted above, a composition may comprise a variant of a native ovarian carcinoma protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native ovarian carcinoma protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with ovarian carcinoma protein-specific antisera may be enhanced or unchanged, relative to the native ovarian carcinoma protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native ovarian carcinoma protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with ovarian carcinoma protein-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

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Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity to the native polypeptide. Preferably, a variant contains conservative substitutions. "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells

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include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions.

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Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises one polypeptide as described herein and a known tumor antigen, such as an ovarian carcinoma protein or a variant of such a protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused

protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

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The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen present cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

Binding Agents

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The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to an ovarian carcinoma protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to an ovarian carcinoma protein if it reacts at a detectable level (within, for example, an ELISA) with an ovarian carcinoma protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a "complex" is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10³ L/mol. The binding constant maybe determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as ovarian cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a ovarian carcinoma antigen will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological

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samples (e.g., blood, sera, leukophoresis, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

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Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the

desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

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Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ⁹⁰Y, ¹²³I, ¹²⁵I, ¹³¹I, ¹⁸⁶Re, ¹⁸⁸Re, ²¹¹At, and ²¹²Bi. Preferred drugs include

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methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

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A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of

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derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

Also provided herein are anti-idiotypic antibodies that mimic an immunogenic portion of an ovarian carcinoma protein. Such antibodies may be raised against an antibody, or antigen-binding fragment thereof, that specifically binds to an

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immunogenic portion of an ovarian carcinoma protein, using well known techniques. Anti-idiotypic antibodies that mimic an immunogenic portion of an ovarian carcinoma protein are those antibodies that bind to an antibody, or antigen-binding fragment thereof, that specifically binds to an immunogenic portion of an ovarian carcinoma protein, as described herein.

T Cells

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Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for an ovarian carcinoma protein. Such cells may generally be prepared in vitro or ex vivo, using standard procedures. For example, T cells may be present within 10 (or isolated from) bone marrow, peripheral blood or a fraction of bone marrow or peripheral blood of a mammal, such as a patient, using a commercially available cell separation system, such as the CEPRATETM system, available from CellPro Inc., Bothell WA (see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human animals, cell lines or cultures.

T cells may be stimulated with an ovarian carcinoma polypeptide, polynucleotide encoding an ovarian carcinoma polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, an ovarian carcinoma polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for an ovarian carcinoma polypeptide if the T cells kill target cells coated with an ovarian carcinoma polypeptide or expressing a gene encoding such a polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be

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accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with an ovarian carcinoma polypeptide (200 ng/ml - 100 µg/ml, preferably 100 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells and/or contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-y) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998). T cells that have been activated in response to an ovarian carcinoma polypeptide, polynucleotide or ovarian carcinoma polypeptide-expressing APC may be CD4⁺ and/or CD8⁺. Ovarian carcinoma polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient or a related or unrelated donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to an ovarian carcinoma polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to an ovarian carcinoma polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize an ovarian carcinoma polypeptide. Alternatively, one or more T cells that proliferate in the presence of an ovarian carcinoma polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution. Following expansion, the cells may be administered back to the patient as described, for example, by Chang et al., *Crit. Rev. Oncol. Hematol. 22*:213, 1996.

Pharmaceutical Compositions and Vaccines

Within certain aspects, polypeptides, polynucleotides, binding agents 30 and/or immune system cells as described herein may be incorporated into

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pharmaceutical compositions or vaccines. Pharmaceutical compositions comprise one or more such compounds or cells and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds or cells and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the compound is incorporated; see e.g., Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., PNAS 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., PNAS 91:215-219, 1994; Kass-Eisler et al.,

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PNAS 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

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While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier 10 will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. 15 For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109. 20

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune

interleukin-2, -7, or -12, may also be used as adjuvants.

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responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI), Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ), alum, biodegradable microspheres, monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or

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Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). Also preferred is AS-2 (SmithKline Beecham). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO

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96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (i.e., a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects per se and/or to be immunologically compatible with the receiver (i.e., matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to

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be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (see Timmerman and Levy, Ann. Rev. Med. 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate in situ, with marked cytoplasmic processes (dendrites) visible in vitro) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells in vivo or ex vivo, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (see Zitvogel et al., Nature Med. 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80 and CD86).

APCs may generally be transfected with a polynucleotide encoding a ovarian carcinoma antigen (or portion or other variant thereof) such that the antigen, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Cancer Therapy

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In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as ovarian cancer. Within such 20 methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a 25 cancer or to treat a patient afflicted with a cancer. Within certain preferred embodiments, a patient is afflicted with ovarian cancer. Such cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration 30 of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the in vivo stimulation of the endogenous

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host immune system to react against tumors with the administration of immuno

response-modifying agents (such as tumor vaccines, bacterial adjuvants and/or

cytokines).

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Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigenpresenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth in vitro, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition in vivo are well known in the art. Such in vitro culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system.

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Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

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Alternatively, a vector expressing a polypeptide recited herein may be introduced into stem cells taken from a patient and clonally propagated *in vitro* for autologous transplant back into the same patient.

Routes and frequency of administration, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration), orally or in the bed of a resected tumor. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level.. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical

outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to an ovarian carcinoma antigen generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

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Screens for Identifying Secreted Ovarian Carcinoma Antigens

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The present invention provides methods for identifying secreted tumor antigens. Within such methods, tumors are implanted into immunodeficient animals such as SCID mice and maintained for a time sufficient to permit secretion of tumor antigens into serum. In general, tumors may be implanted subcutaneously or within the gonadal fat pad of an immunodeficient animal and maintained for 1-9 months, preferably 1-4 months. Implantation may generally be performed as described in WO 97/18300. The serum containing secreted antigens is then used to prepare antisera in immunocompetent mice, using standard techniques and as described herein. Briefly, 50-100 µL of sera (pooled from three sets of immunodeficient mice, each set bearing a different SCID-derived human ovarian tumor) may be mixed 1:1 (vol:vol) with an appropriate adjuvant, such as RIBI-MPL or MPL + TDM (Sigma Chemical Co., St. Louis, MO) and injected intraperitoneally into syngeneic immunocompetent animals at monthly intervals for a total of 5 months. Antisera from animals immunized in such a manner may be obtained by drawing blood after the third, fourth and fifth immunizations. The resulting antiserum is generally pre-cleared of E. coli and phage antigens and used (generally following dilution, such as 1:200) in a serological expression screen.

The library is typically an expression library containing cDNAs from one or more tumors of the type that was implanted into SCID mice. This expression library may be prepared in any suitable vector, such as λ-screen (Novagen). cDNAs that encode a polypeptide that reacts with the antiserum may be identified using standard techniques, and sequenced. Such cDNA molecules may be further characterized to

evaluate expression in tumor and normal tissue, and to evaluate antigen secretion in patients.

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The methods provided herein have advantages over other methods for tumor antigen discovery. In particular, all antigens identified by such methods should be secreted or released through necrosis of the tumor cells. Such antigens may be present on the surface of tumor cells for an amount of time sufficient to permit targeting and killing by the immune system, following vaccination.

Methods for Detecting Cancer

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In general, a cancer may be detected in a patient based on the presence of one or more ovarian carcinoma proteins and/or polynucleotides encoding such proteins in a biological sample (such as blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as ovarian cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of protein that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, an ovarian carcinoma-associated sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding

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agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length ovarian carcinoma proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about $10\,\mu g$, and preferably about $100\,ng$ to about $1\,\mu g$, is sufficient to immobilize an adequate amount of binding agent.

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Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

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In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20^{TM} (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with ovarian cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over

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a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20TM. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibodypolypeptide complex for an amount of time sufficient to detect the bound polypeptide.

An appropriate amount of time may generally be determined by assaying the level of
binding that occurs over a period of time. Unbound detection reagent is then removed
and bound detection reagent is detected using the reporter group. The method employed
for detecting the reporter group depends upon the nature of the reporter group. For
radioactive groups, scintillation counting or autoradiographic methods are generally
appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups
and fluorescent groups. Biotin may be detected using avidin, coupled to a different
reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme
reporter groups may generally be detected by the addition of substrate (generally for a
specific period of time), followed by spectroscopic or other analysis of the reaction
products.

To determine the presence or absence of a cancer, such as ovarian cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity)

that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

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Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use ovarian carcinoma polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such ovarian carcinoma protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with an ovarian carcinoma protein in a biological sample. Within certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with an ovarian carcinoma protein, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with an ovarian carcinoma protein (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of ovarian carcinoma protein to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding an ovarian carcinoma protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of an ovarian carcinoma protein cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the ovarian carcinoma protein. The amplified cDNA is then separated and detected using techniques well

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known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding an ovarian carcinoma protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

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To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding an ovarian carcinoma protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence provided herein. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample such as a biopsy tissue and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, ovarian carcinoma proteins and polynucleotides encoding such proteins may be used as markers for monitoring the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple ovarian carcinoma protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

Diagnostic Kits

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The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to an ovarian carcinoma protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain

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a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding an ovarian carcinoma protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding an ovarian carcinoma protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding an ovarian carcinoma protein.

The following Examples are offered by way of illustration and not by way of limitation.

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EXAMPLES

EXAMPLE 1

IDENTIFICATION OF REPRESENTATIVE OVARIAN CARCINOMA PROTEIN CDNAS

This Example illustrates the identification of cDNA molecules encoding ovarian carcinoma proteins.

Anti-SCID mouse sera (generated against sera from SCID mice carrying late passage ovarian carcinoma) was pre-cleared of E. coli and phage antigens and used at a 1:200 dilution in a serological expression screen. The library screened was made from a SCID-derived human ovarian tumor (OV9334) using a directional RH oligo(dT) priming cDNA library construction kit and the λ Screen vector (Novagen). A bacteriophage lambda screen was employed. Approximately 400,000 pfu of the amplified OV9334 library were screened.

196 positive clones were isolated. Certain sequences that appear to be novel are provided in Figures 1A-1S and SEQ ID NO:1 to 71. Three complete insert sequences are shown in Figures 2A-2C (SEQ ID NO:72 to 74). Other clones having known sequences are presented in Figures 15A-15EEE (SEQ ID NO:82 to 310). Database searches identified the following sequences that were substantially identical to the sequences presented in Figures 15A-15EEE.

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These clones were further characterized using microarray technology to

determine mRNA expression levels in a variety of tumor and normal tissues. Such
analyses were performed using a Synteni (Palo Alto, CA) microarray, according to the
manufacturer's instructions. PCR amplification products were arrayed on slides, with
each product occupying a unique location in the array. mRNA was extracted from the
tissue sample to be tested, reverse transcribed and fluorescent-labeled cDNA probes
were generated. The microarrays were probed with the labeled cDNA probes and the
slides were scanned to measure fluorescence intensity. Data was analyzed using
Synteni's provided GEMtools software. The results for one clone (13695, also referred
to as O8E) are shown in Figure 3.

EXAMPLE 2

IDENTIFICATION OF OVARIAN CARCINOMA CDNAs USING MICROARRAY TECHNOLOGY

This Example illustrates the identification of ovarian carcinoma polynucleotides by PCR subtraction and microarray analysis. Microarrays of cDNAs were analyzed for ovarian tumor-specific expression using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997).

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A PCR subtraction was performed using a tester comprising cDNA of four ovarian tumors (three of which were metastatic tumors) and a driver of cDNA form five normal tissues (adrenal gland, lung, pancreas, spleen and brain). cDNA fragments recovered from this subtraction were subjected to DNA microarray analysis where the fragments were PCR amplified, adhered to chips and hybridized with fluorescently labeled probes derived from mRNAs of human ovarian tumors and a variety of normal human tissues. In this analysis, the slides were scanned and the fluorescence intensity was measured, and the data were analyzed using Synteni's GEMtools software. In general, sequences showing at least a 5-fold increase in expression in tumor cells (relative to normal cells) were considered ovarian tumor antigens. The fluorescent results were analyzed and clones that displayed increased expression in ovarian tumors were further characterized by DNA sequencing and database searches to determine the novelty of the sequences.

Using such assays, an ovarian tumor antigen was identified that is a splice fusion between the human T-cell leukemia virus type I oncoprotein TAX (see Jin et al., Cell 93:81-91, 1998) and an extracellular matrix protein called osteonectin. A splice junction sequence exists at the fusion point. The sequence of this clone is presented in Figure 4 and SEQ ID NO:75. Osteonectin, unspliced and unaltered, was also identified from such assays independently.

Further clones identified by this method are referred to herein as 3f, 6b, 8e, 8h, 12c and 12h. Sequences of these clones are shown in Figures 5 to 9 and SEQ ID NO:76 to 81. Microarray analyses were performed as described above, and are presented in Figures 10 to 14. A full length sequence encompassing clones 3f, 6b, 8e

and 12h was obtained by screening an ovarian tumor (SCID-derived) cDNA library. This 2996 base pair sequence (designated O772P) is presented in SEQ ID NO:311, and the encoded 914 amino acid protein sequence is shown in SEQ ID NO:312. PSORT analysis indicates a Type 1a transmembrane protein localized to the plasma membrane.

In addition to certain of the sequences described above, this screen identified the following sequences which are described in detail in Table 1:

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Table 1

Sequence	Comments
OV4vG11 (SEQ ID NO:313)	human clone 1119D9 on chromosome 20p12
OV4vB11 (SEQ ID NO:314)	human UWGC:y14c094 from chromosome 6p21
OV4vD9 (SEQ ID NO:315)	human clone 1049G16 chromosome 20q12-13.2
OV4vD5 (SEQ ID NO:316)	human KIAA0014 gene
OV4vC2 (SEQ ID NO:317)	human KIAA0084 gene
OV4vF3 (SEQ ID NO:318)	human chromosome 19 cosmid R31167
OV4VC1 (SEQ ID NO:319)	novel
OV4vH3 (SEQ ID NO:320)	novel
OV4vD2 (SEQ ID NO:321)	novel
O815P (SEQ ID NO:322)	novel
OV4vC12 (SEQ ID NO:323)	novel
OV4vA4 (SEQ ID NO:324)	novel
OV4vA3 (SEQ ID NO:325)	novel
OV4v2A5 (SEQ ID NO:326)	novel
O819P (SEQ ID NO:327)	novel
O818P (SEQ ID NO:328)	novel
O817P (SEQ ID NO:329)	novel
O816P (SEQ ID NO:330)	novel
Ov4vC5 (SEQ ID NO:331)	novel
21721 (SEQ ID NO:332)	human lumican
21719 (SEQ ID NO:333)	human retinoic acid-binding protein II
21717 (SEQ ID NO:334)	human26S proteasome ATPase subunit
21654 (SEQ ID NO:335)	human copine I
21627 (SEQ ID NO:336)	human neuron specific gamma-2 enolase

Sequence	Comments	
21623 (SEQ ID NO:337)	human geranylgeranyl transferase II	
21621 (SEQ ID NO:338)	human cyclin-dependent protein kinase	
21616 (SEQ ID NO:339)	human prepro-megakaryocyte potentiating factor	
21612 (SEQ ID NO:340)	human UPH1	
21558 (SEQ ID NO:341)	human RalGDS-like 2 (RGL2)	
21555 (SEQ ID NO:342)	human autoantigen P542	
21548 (SEQ ID NO:343)	human actin-related protein (ARP2)	
21462 (SEQ ID NO:344)	human huntingtin interacting protein	
21441 (SEQ ID NO:345)	human 90K product (tumor associated antigen)	
21439 (SEQ ID NO:346)	human guanine nucleotide regulator protein (tim1)	
21438 (SEQ ID NO:347)	human Ku autoimmune (p70/p80) antigen	
21237 (SEQ ID NO:348)	human S-laminin	
21436 (SEQ ID NO:349)	human ribophorin I	
21435 (SEQ ID NO:350)	human cytoplasmic chaperonin hTRiC5	
21425 (SEQ ID NO:351)	humanEMX2	
21423 (SEQ ID NO:352)	human p87/p89 gene	
21419 (SEQ ID NO:353)	human HPBRII-7	
21252 (SEQ ID NO:354)	human T1-227H	
21251 (SEQ ID NO:355)	human cullin I	
21247 (SEQ ID NO:356)	kunitz type protease inhibitor (KOP)	
21244-1 (SEQ ID NO:357)	human protein tyrosine phosphatase receptor F (PTPRF)	
21718 (SEQ ID NO:358)	human LTR repeat	
OV2-90 (SEQ ID NO:359)	novel	
Human zinc finger (SEQ ID NO:360)		
Human polyA binding protein (SEQ ID NO:361)		
Human pleitrophin (SEQ ID NO:362)		
Human PAC clone 278C19 (SEQ ID NO:363)		
Human LLRep3 (SEQ ID NO:364)		
Human Kunitz type protease inhib (SEQ ID NO:365)		
Human KIAA0106 gene (SEQ ID NO:366)		
Human keratin (SEQ ID NO:367)		
Human HIV-1TAR (SEQ ID NO:368)		
Human glia derived nexin (SEQ ID NO:369)		

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Sequence	Comments	
Human fibronectin (SEQ ID NO:370)		
Human ECMproBM40 (SEQ ID NO:371)		
Human collagen (SEQ ID NO:372)		
Human alpha enolase (SEQ ID NO:373)		
Human aldolase (SEQ ID NO:374)		
Human transf growth factor BIG H3 (SEQ ID NO:375)		
Human SPARC osteonectin (SEQ ID NO:376)		
Human SLP1 leucocyte protease (SEQ ID NO:377)		
Human mitochondrial ATP synth (SEQ ID NO:378)		
Human DNA seq clone 461P17 (SEQ ID NO:379)		
Human dbpB pro Y box (SEQ ID NO:380)		
Human 40 kDa keratin (SEQ ID NO:381)		
Human arginosuccinate synth (SEQ ID NO:382)		
Human acidic ribosomal phosphoprotein (SEQ ID NO:383)		
Human colon carcinoma laminin binding pro (SEQ ID NO:384)		

This screen further identified multiple forms of the clone O772P, referred to herein as 21013, 21003 and 21008. PSORT analysis indicates that 21003 (SEQ ID NO:386; translated as SEQ ID NO:389) and 21008 (SEQ ID NO:387; translated as SEQ ID NO:390) represent Type 1a transmembrane protein forms of O772P. 21013 (SEQ ID NO:385; translated as SEQ ID NO:388) appears to be a truncated form of the protein and is predicted by PSORT analysis to be a secreted protein.

Additional sequence analysis resulted in a full length clone for O8E (2627 bp, which agrees with the message size observed by Northern analysis; SEQ ID NO:391). This nucleotide sequence was obtained as follows: the original O8E sequence (OrigO8Econs) was found to overlap by 33 nucleotides with a sequence from an EST clone (IMAGE#1987589). This clone provided 1042 additional nucleotides upstream of the original O8E sequence. The link between the EST and O8E was confirmed by sequencing multiple PCR fragments generated from an ovary primary tumor library using primers to the unique EST and the O8E sequence (ESTxO8EPCR). Full length status was further indicated when anchored PCR from the ovary tumor library gave

several clones (AnchoredPCR cons) that all terminated upstream of the putative start methionine, but failed to yield any additional sequence information. Figure 16 presents a diagram that illustrates the location of each partial sequence within the full length O8E sequence.

Two protein sequences may be translated from the full length O8E. For "a" (SEQ ID NO:393) begins with a putative start methionine. A second form "b" (SEQ ID NO:392) includes 27 additional upstream residues to the 5' end of the nucleotide sequence.

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EXAMPLE 3

This example discloses the identification and characterization of antibody epitopes recognized by the O8E polyclonal anti-sera.

Rabbit anti-sera was raised against E. coli derived O8E recombinant protein and tested for antibody epitope recognition against 20 or 21 mer peptides that correspond to the O8E amino acid sequence. Peptides spanning amino acid regions 31 to 65, 76 to 110, 136 to 200 and 226 to 245 of the full length O8E protein were recognized by an acid eluted peak and/or a salt eluted peak from affinity purified anti-O8E sera. Thus, the corresponding amino acid sequences of the above peptides constitute the antibody epitopes recognized by affinity purified anti-O8E antibodies.

ELISA analysis of anti-08E rabbit sera is shown in Figure 23, and ELISA analysis of affinity purified rabbit anti-08E polyclonal antibody is shown in Figure 24.

For epitope mapping, 20 or 21 mer peptides corresponding to the O8E protein were synthesized. For antibody affinity purification, rabbit anti-O8E sera was run over an O8E-sepharose column, then antibody was eluted with a salt buffer containing 0.5 M NaCl and 20 mM PO₄, followed by an acid elution step using 0.2 M Glycine, pH 2.3. Purified antibody was neutralized by the addition of 1M Tris, pH 8 and buffer exchanged into phosphate buffered saline (PBS). For enzyme linked immunosorbant assay (ELISA) analysis, O8E peptides and O8E recombinant protein were coated onto 96 well flat bottom plates at 2 μg/ml for 2 hours at room temperature (RT). Plates were then washed 5 times with PBS + 0.1 % Tween 20 and blocked with PBS + 1 % bovine serum albumin (BSA) for 1 hour. Affinity purified anti-O8E antibody, either an acid or salt eluted fraction, was then added to the wells at 1 μg/ml

and incubated at RT for 1 hr. Plates were again washed, followed by the addition of donkey anti-rabbit-Ig-horseradish peroxidase (HRP) antibody for 1 hour at RT. Plates were washed, then developed by the addition of the chromagenic substrate 3, 3', 5, 5'-tetramethylbenzidine (TMB) (described by Bos et al., J. of Immunoassay 2:187-204 (1981); available from Sigma (St. Louis, MO)). The reaction was incubated 15 minutes at RT and then stopped by the addition of 1 N H₂SO₄. Plates were read at an optical density of 450 (OD450) in an automated plate reader. The sequences of peptides corresponding to the OE8 antibody epitopes are disclosed herein as SEQ ID NO: 394-415. Antibody epitopes recognized by the O8E polyclonal anti-sera are disclosed herein in Figure 17.

EXAMPLE 4

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This example discloses IHC analysis of O8E expression in ovarian cancer tissue samples.

For immunohistochemistry studies, paraffin-embedded formalin fixed ovarian cancer tissue was sliced into 8 micron sections. Steam heat induced epitope retrieval (SHIER) in 0.1 M sodium citrate buffer (pH 6.0) was used for optimal staining conditions. Sections were incubated with 10% serum/PBS for 5 minutes. Primary antibody (anti-O8E rabbit affinity purified polyclonal antibody) was added to each section for 25 min followed by a 25 min incubation with an anti-rabbit biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 min incubations with hydrogen peroxidase. The avidin biotin complex/horse radish peroxidase system was used along with DAB chromogen to visualize antigen expression. Slides were counterstained with hematoxylin. One (papillary serous carcinoma) of six ovarian cancer tissue sections displayed O8E immunoreactivity. Upon optimization of the staining conditions, 4/5 ovarian cancer samples stained positive using the O8E polyclonal antibody. O8E expression was localized to the plasma membrane.

Six ovarian cancer tissues were analyzed with the anti-O8E rabbit polyclonal antibody. One (papillary serous carcinoma) of six ovarian cancer tissue samples stained positive for O8E expression. O8E expression was localized to the surface membrane.

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EXAMPLE 5

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This example discloses O8E peptides that are predicted to bind HLA-A2 and to be immunogenic for CD8 T cell responses in humans.

Potential HLA-A2 binding peptides of O8E were predicted by using the full-length open-reading frame (ORF) from O8E and running it through "Episeek," a program used to predict MHC binding peptides. The program used is based on the algorithm published by Parker, K.C. et al., J. Immunol. 152(1):163-175 (1994) (incorporated by reference herein in its entirety). 10-mer and 9-mer peptides predicted to bind HLA-0201 are disclosed herein as SEQ ID NO: 416-435 and SEQ ID NO: 436-455, respectively.

EXAMPLE 6

This example discloses O8E cell surface expression measured by fluoresence activated cell sorting.

For FACS analysis, cells were washed with ice cold staining buffer (PBS/1% BSA/azide). Next, the cells were incubated for 30 minutes on ice with 10 micrograms/ml of affinity purified rabbit anti-B305D polyclonal antibody. The cells were washed 3 times with staining buffer and then incubated with a 1:100 dilution of a goat anti-rabbit Ig (H+L)-FITC reagent (Southern Biotechnology) for 30 minutes on ice. Following 3 washes, the cells were resuspended in staining buffer containing prodium iodide, a vital stain that allows for identification of permeable cells, and analyzed by FACS. O8E surface expression was confirmed on SKBR3 breast cancer cells and HEK293 cells that stably overexpress the cDNA for O8E. Neither MB415 cells nor HEK293 cells stably transfected with a control irrelevant plasmid DNA showed surface expression of O8E (Figures 18 and 19).

25 EXAMPLE 7

This example further evaluates the expression and surface localization of O8E.

For expression and purification of antigen used for immunization, O8E expressed in an E. coli recombinant expression system was grown overnight in LB Broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning,

10 ml of the overnight culture was added to 500 ml of 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nanometers) of the culture reached 0.4-0.6 the cells were induced with IPTG (1 mM). 4 hours after induction with IPTG the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty milliliters of lysis buffer was added to the cell pellets and vortexed. To break open the E. coli cells, this mixture was then run through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For protein that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0 , 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification. As a final purification step, a strong anion exchange resin such as Hi-Prep Q (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off of the column with an increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. This material was then evaluated for acceptable purity as determined by SDS-PAGE or HPLC, concentration as determined by Lowry assay or Amino Acid Analysis, identity as determined by amino terminal protein sequence, and endotoxin level as determined by the Limulus (LAL) assay. The

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proteins were then vialed after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

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For generation of polyclonal anti-sera, 400 micrograms of each prostate antigen was combined with 100 micrograms of muramyldipeptide (MDP). Equal volume of Incomplete Freund's Adjuvant (IFA) was added and then mixed. Every four weeks animals were boosted with 100 micrograms of antigen mixed with an equal volume of IFA. Seven days following each boost the animal was bled. Sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

For characterization of polyclonal antisera, 96 well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) at 4°C for 20 hrs. 250 microliters of BSA blocking buffer was added to the wells and incubated at RT for 2 hrs. Plates were washed 6 times with PBS/0.01% tween. Anti-O8E rabbit sera or affinity purified anti-O8e antibody was diluted in PBS. Fifty microliters of diluted antibody was added to each well and incubated at RT for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at RT for 30 min. Plates were washed as described above and 100 microliters of TMB microwell Peroxidase Substrate was added to each well. Following a 15 minute incubation in the dark at room temperature the colorimetric reaction was stopped with 100 microliters of 1N H2SO4 and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity to the O8E antigen.

For recombinant expression in mammalian HEK293 cells, full length O8E cDNA was subcloned into the mammalian expression vectors pcDNA3.1+ and pCEP4 (Invitrogen) which were modified to contain His and FLAG epitope tags, respectively. These constructs were transfected into HEK293 cells (ATCC) using Fugene 6 reagent (Roche). Briefly, HEK293 cells were plated at a density of 100,000 cells/ml in DMEM (Gibco) containing 10% FBS (Hyclone) and grown overnight. The following day, 2 ul of Fugene6 was added to 100 ul of DMEM containing no FBS and incubated for 15 minutes at room temperature. The Fugene6/DMEM mixture was then added to lug of O8E/pCEP4 or O8E/pcDNA3.1 plasmid DNA and incubated for 15 minutes at room temperature. The Fugene/DNA mix was then added to the HEK293

cells and incubated for 48-72 hrs at 37oC with 7% CO2. Cells were rinsed with PBS then collected and pelleted by centrifugation. For Western blot analysis, whole cell lysates were generated by incubating the cells in Triton-X100 containing lysis buffer for 30 minutes on ice. Lysates were then cleared by centrifugation at 10,000rpm for 5 minutes at 4 C. Samples were diluted with SDS-PAGE loading buffer containing beta-mercaptoethanol, then boiled for 10 minutes prior to loading the SDS-PAGE gel. Protein was transferred to nitrocellulose and probed using anti-O8E rabbit polyclonal sera #2333L at a dilution of 1:750. The blot was revealed with a goat anti-rabbit Ig coupled to HRP followed by incubation in ECL substrate.

For FACS analysis, cells were washed further with ice cold staining buffer (PBS+1%BSA+Azide). Next, the cells were incubated for 30 minutes on ice with 10ug/ml of Protein A purified anti-O8E polyclonal sera. The cells were washed 3 times with staining buffer and then incubated with a 1:100 dilution of a goat anti-rabbit Ig(H+L)-FITC reagent (Southern Biotechnology) for 30 minutes on ice. Following 3 washes, the cells were resuspended in staining buffer containing Propidium Iodide (PI), a vital stain that allows for the identification of permeable cells, and analyzed by FACS.

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From these experiments, the results of which are illustrated in Figures 20-21, O8E expression was detected on the surface of transfected HEK293 cells and SKBR3 cells by FACS analysis using rabbit anti-O8E sera. Expression was also detected in transfected HEK293 cell lysates by Western blot analysis (Figure 22).

EXAMPLE 8

GENERATION AND CHARACTERIZATION OF ANTI-O8E MABS.

Mouse monoclonal antibodies were raised against E. coli derived O8E proteins as follows. A/J mice were immunized intraperitoneally (IP) with Complete Freund's Adjuvant (CFA) containing 50 µg recombinant O8E, followed by a subsequent IP boost with Incomplete Freund's Adjuvant (IFA) containing 10µg recombinant O8E protein. Three days prior to removal of the spleens, the mice were immunized intravenously with approximately 50µg of soluble O8E recombinant protein. The spleen of a mouse with a positive titer to O8E was removed, and a single-cell suspension made and used for fusion to SP2/0 myeloma cells to generate B cell

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hybridomas. The supernatants from the hybrid clones were tested by ELISA for specificity to recombinant O8E, and epitope mapped using peptides that spanned the entire O8E sequence. The mAbs were also tested by flow cytometry for their ability to detect O8E on the surface of cells stably transfected with O8E and on the surface of a breast tumor cell line.

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For ELISA analysis, 96 well plates were coated with either recombinant O8E protein or overlapping 20-mer peptides spanning the entire O8E molecule at a concentration of either 1-2µg/ml or 10µg/ml, respectively. After coating, the plates were washed 5 times with washing buffer (PBS + 0.1% Tween-20) and blocked with PBS containing 0.5% BSA, 0.4% Tween-20. Hybrid supernatants or purified mAbs were then added and the plates incubated for 60 minutes at room temperature. The plates were washed 5 times with washing buffer and the secondary antibody, donkeyanti mouse Ig linked to horseradish peroxidase (HRP)(Jackson ImmunoResearch), was added for 60 minutes. The plates were again washed 5 times in washing buffer, followed by the addition of the peroxidase substrate. Of the hybridoma clones generated, 15 secreted mAbs that recognized the entire O8E protein. Epitope mapping revealed that of these 15 clones, 14 secreted mAbs that recognized the O8E amino acid residues 61-80 and one clone secreted a mAb that recognized amino acid residues 151-170.

For flow cytometric analysis, HEK293 cells which had been stably transfected with O8E and SKBR3 cells which express O8E mRNA, were harvested and washed in flow staining buffer (PBS+1%BSA+Azide). The cells were incubated with the supernatant from the mAb hybrids for 30 minutes on ice followed by 3 washes with staining buffer. The cells were incubated with goat-anti mouse Ig-FITC for 30 minutes on ice, followed by three washes with staining buffer before being resuspended in wash buffer containing propidium iodide. Flow cytometric analysis revealed that 15/15 mAbs were able to detect O8E protein expressed on the surface of O8E-transfected HEK293 cells. 6/6 mAbs tested on SKBR3 cells were able to recognize surface expressed O8E.

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EXAMPLE 9

EXTENDED DNA AND PROTEIN SEQUENCE ANALYSIS OF SEQUENCE O772P

A full-length sequence encompassing clones 3f, 6b, 8e, and 12 was obtained by screening an ovarian tumor (SCID-derived) cDNA library described in detail in Example 2. This 2996 base pair sequence, designated O772P, is presented in SEQ ID NO: 311, and the encoded 914 amino acid protein sequence is shown in SEQ ID NO: 312. The DNA sequence O772P was searched against public databases including Genbank and showed a significant hit to Genbank Accession number AK024365 (SEQ ID NO: 457). This Genbank sequence was found to be 3557 base pairs in length and encodes a protein 1156 amino acids in length (SEQ ID NO: 459). A truncated version of this sequence, residues 25-3471, in which residue 25 corresponds to the first ATG initiation codon in the Genbank sequence, (SEQ ID NO: 456), encodes a protein that is 1148 amino acids in length (SEQ ID NO: 458). The published DNA sequence (SEQ ID NO: 457) differs from O772P in that it has a 5 base pair insertion corresponding to bases 958-962 of SEQ ID NO: 457. This insertion results in a frame shift such that SEQ ID NO: 457 encodes an additional N-terminal protein sequence relative to O772P (SEQ ID NO: 312). In addition, O772P encodes a unique N-terminal portion contained in residues 1-79 (SEQ ID NO: 460). The N-terminal portion of SEQ ID NO: 456, residues 1-313, also contains unique sequence and is listed as SEQ ID NO: 461.

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EXAMPLE 10

THE GENERATION OF POLYCLONAL ANTIBODIES FOR IMMUNOHISTOCHEMISTRY
AND FLOW CYTOMETRIC ANALYSIS OF THE CELL ASSOCIATED EXPRESSION
PATTERN OF MOLECULE O772P

The O772P molecule was identified in Examples 2 and 9 of this application. To evaluate the subcellular localization and specificity of antigen expression in various tissues, polyclonal antibodies were generated against O772P. To produce these antibodies, O772P-1 (amino acids 44-772 of SEQ ID NO:312) and O772P-2 (477-914 of SEQ ID NO:312) were expressed in an E. coli recombinant expression system and grown overnight at 37°C in LB Broth. The following day, 10ml

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of the overnight culture was added to 500ml of 2xYT containing the appropriate antibiotics. When the optical density of the cultures (560 nanometers) reached 0.4-0.6 the cells were induced with IPTG. Following induction, the cells were harvested, washed, lysed and run through a French Press at a pressure of 16000 psi. The cells were then centrifuged and the pellet checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localize to the cell pellet, the pellet was resuspended in 10mM Tris, pH 8.0, 1% CHAPS and the inclusion body pellet washed and centrifuged. The washed inclusion body was solubilized with either 8M urea or 6M guanidine HCL containing 10mM Tris, pH 8.0, plus 10mM imidazole. The solubilized protein was then added to 5ml of nickel-chelate resin (Qiagen) and incubated for 45 minutes at room temperature.

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Following the incubation, the resin and protein mixture was poured through a column and the flow through collected. The column was washed with 10-20 column volumes of buffer and the antigen eluted using 8M urea, 10mM Tris, pH 8.0, and 300 mM imidazole and collected in 3ml fractions. SDS-PAGE was run to determine which fractions to pool for further purification. As a final purification step, a strong anion exchange resin was equilibrated with the appropriate buffer and the pooled fractions were loaded onto the column. Each antigen was eluted from the column with an increasing salt gradient. Fractions were collected and analyzed by a SDS-PAGE to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10mM Tris, pH 8.0, and the resulting protein was submitted for quality control for final release. The release criteria were: (a) purity as determined by SDS-PAGE or HPLC, (b) concentration as determined by Lowry assay or Amino Acid Analysis, (c) identity as determined by amino terminal protein, and (d) endotoxin levels as determined by the Limulus (LAL) assay. The proteins were then filtered through a 0.22 µM filter and frozen until needed for immunizations.

To generate polyclonal antisera, 400µg of O772P-1 or O772P-2 was combined with 100µg of muramyldipeptide (MDP). The rabbits were immunized every 4 weeks with 100µg of antigen mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animals were bled and sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

To characterize the antisera, 96 well plates were coated with antigen followed by blocking with BSA. Rabbit sera was diluted in PBS and added to each well. The plates were then washed, and goat anti-rabbit horseradish peroxidase (HRP). The plates were again washed and TMB microwell Peroxidase Substrate was added. Following this incubation, the colormetric reaction was stopped and the plates read immediately at 450nm. All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

Immunohistochemistry analysis of O772P expression was performed on paraffin-embedded formalin fixed tissue. O772P was found to be expressed in normal ovary and ovarian tumor, but not in normal heart, kidney, colon, lung or liver. Additionally, immunohistochemistry and flow cytometric analysis indicates that O772P is a plasma membrane-associated molecule. O772P contains 1 plasma transmembrane domain predicted to be encoded by amino acids 859-880. The N-terminus of O772P is extracellular and is encoded by amino acids 1-859, while the C-terminus is intracellular. Sequence analysis shows that there are 17 potential N-linked glycosylation sites.

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EXAMPLE 11

O772P IS EXPRESSED ON THE SURFACE OF PRIMARY OVARIAN TUMOR CELLS

For recombinant expression in mammalian cells, the O772P-21008 (SEQ ID NO:387) and O772P full length cDNA (SEQ ID NO:311 encoding the protein of SEQ ID NO:312) were subcloned into mammalian expression vectors pBIB or pCEP4 respectively. These constructs were transfected into HEK293 cells using Fugene 6 (Roche). The HEK cells were then plated at a density of 100,000 cells/ml in DMEM containing fetal bovine serum (FBS) and grown overnight. The following day, 2μl of Fugene 6 was added to 100μl of DMEM, which contained no FBS, and incubated for 15 minutes at room temperature. The Fugene 6/DMEM mixture was then added to 1μg of O772P/pBIB or O772P/pCEP4 plasmid DNA and incubated for an additional 15 minutes at room temperature. The Fugene 6/DNA mix was then added to the HEK293 cells and incubated for 48-72 hours at 37°C with 7% CO₂. The cells were rinsed and pelleted by centrifugation.

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For Western Blot analysis, whole cell lysates were generated by incubating the cells in lysis buffer followed by clarification by centrifugation. The samples were diluted and run on SDS-PAGE. The gel was then transferred to nitrocellulose and probed using purified anti-O772P-2 rabbit polyclonal antibody. The blot was revealed with a goat anti-rabbit Ig coupled to HRP followed by incubation in ECL substrate. Western Blot analysis revealed that O772P-21008 could be detected in HEK293 cells that had been transfected with O772P.

To determine the cell expression profile of O772P in cells, primary ovarian tumor cells were grown in SCID mice. The cells were retrieved from the mice and analyzed by flow cytometry. Briefly, cells washed in cold staining buffer containing PBS, 1% BSA, and Na Azide. The cells were incubated for 30 minutes with 10µg/ml of purified anti-O772P-1 and O772P-2 polyclonal sera. Following this incubation, the cells were washed three times in staining buffer and incubated with goat anti-rabbit Ig (H+L) conjugated to FITC (Southern Biotechnology). The cells were washed and resuspended in staining buffer containing Propidium Iodide (PI), a vital stain that identifies non-viable cells. The cells were then analyzed using Fluorescence Activated Cell Sorting (FACS). FACS analysis revealed that O772P was present on the cells surface. Surface expression of O772P on tumor cells allows for immune targeting by therapeutic antibodies.

20 EXAMPLE 12

FUNCTIONAL CHARACTERIZATION OF ANTI-O8E MONOCLONAL ANTIBODIES

Mouse monoclonal antibodies (mAb) raised against E. coli derived O8E, as described in Example 8, were tested for their ability to promote O8E antigen internalization. Internalization of the antibody was determined using an in vitro cytotoxicity assay. Briefly, HEK293 and O8E/HEK transfected cells were plated into 96 well plates containing DME plus 10% heat-inactivated FBS in the presence of 50ng/well of purified anti-O8E or control antibodies. The isotype of the anti-O8E mAbs are as follows: 11A6-IgG1/kappa, 15C6-IgG2b/kappa, 18A8-IgG2b/kappa, and 14F1-IgG2a/kappa. W6/32 is a pan anti-human MHC class I mouse monoclonal antibody that serves as a positive control, and two irrelevant mAbs, Ir-Pharm and Ir-

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Crxa were included as negative controls. Following incubation with the O8E specific antibodies or the relevant controls antibodies, the mAb-zap, a goat anti-mouse Igsaporin conjugated secondary antibody (Advanced Targeting Systems) was added at a concentration of 100ng/ml to half of the wells, and the plates were incubated for 48 to 72 hours at 37°C in a 7% CO₂ incubator. This assay takes advantage of the toxic nature of saporin, a ribozyme inactivating protein, which when internalized has a cytotoxic effect. Following incubation with the mAb-zap, internalization was quantitated by the addition of MTS reagent, followed by reading the OD490 of the plate on a microplate ELISA reader. Figure 25 depicts the results from these assays. The top panel represents HEK cells that have not been transfected with O8E and therefore O8E antibody should not bind and be internalized. Levels of proliferation were the same in all samples whether they were incubated with or without the mAb-zap, with the exception of the positive control Ab, W6/32. The lower panel represents cells that have been transfected with O8E and therefore should bind O8E specific antibodies. Antibodies from the hybridomas 11H6, 14F1, and 15C6, which recognize the amino acids 61-80 of O8E were able to promote internalization of the O8E surface protein as measured by decreased levels of proliferation due to the toxic nature of the mAb-zap (See Figure 25). The antibody generated by the hybridoma 18A8, which recognizes amino acids 151-170 of O8E, was unable to promote internalization as determined by normal levels of proliferation either in the absence or presence of the mAb-zap.

EXAMPLE 13

CHARACTERIZATION OF THE OVARIAN TUMOR ANTIGEN, O772P

The cDNA and protein sequences for multiple forms of the ovarian tumor antigen O772P have been described in the above (e.g., Examples 2 and 9). A Genbank search indicated that O772P has a high degree of similarity with FLJ14303 (Accession # AK024365; SEQ ID NO:457 and 463). Protein sequences corresponding to O772P and FLJ14303 are disclosed in SEQ ID NO:478 and 479, respectively. FLJ14303 was identical to the majority of O772P, with much of the 3'-end showing 100% homology. However, the 5'-end of FLJ14303 was found to extend further 5' than O772P. In addition, FLJ14303 contained a 5 bp insert (SEO ID NO:457) resulting in a

frame shift of the amino-terminus protein sequence such that FLJ14303 utilizes a different starting methionine than O772P and therefore encodes a different protein. This insertion was present in the genomic sequence and seen in all EST clones that showed identity to this region, suggesting that FLJ14303 (SEQ ID NO:457) represents a splice variant of O772P, with an ORF that contains an extended and different amino-terminus. The additional 5'-nucleotide sequence included repeat sequences that were identified during the genomic mapping of O772P. The 5'-end of O772P and the corresponding region of FLJ14303 showed between 90-100% homology. Taken together, this suggests that O772P and FLJ14303 are different splice variants of the same gene, with different unique repeat sequences being spliced into the 5'-end of the gene.

The identification of an additional ten or more repeat sequences within the same region of chromosome 19, indicates that there may be many forms of O772P, each with a different 5'-end, due to differential splicing of different repeat sequences. Northern blot analysis of O772P demonstrated multiple O772P-hybridizing transcripts of different sizes, some in excess 10kb.

Upon further analysis, 13 additional O772P-related sequences were identified, the cDNA and amino acid sequences of which are described in Table 2.

Table 2

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SEQ ID NO:	Description	Transmembrane Domains
464	LS #1043400.1 (cDNA)	nd
465	LS #1043400.10 (cDNA)	0
466	LS #1043400.11 (cDNA)	2
467	LS #1043400.12 (cDNA)	2
468	LS #1043400.2 (cDNA)	nd
469	LS #1043400.3 (cDNA)	
470	LS #1043400.5 (cDNA)	nd
471	LS #1043400.8 (cDNA)	1
472	LS #1043400.9 (cDNA)	0

473	LS #1043400.6 (cDNA)	nd
474	LS #1043400.7 (cDNA)	nd
475	LS #1043400.4 (cDNA)	nd
476	LS #1397610.1 (cDNA)	0
477	1043400.10 Novel 5' (cDNA)	•
480	LS #1043400.9 (amino acid)	-
481	LS #1043400.8B (amino acid)	-
j	Contains a transmembrane	
	domain	
482	LS #1043400.8A (amino acid)	-
483	LS #1043400.12 (amino acid)	
:	Contains a transmembrane	
	domain	
484	LS #1043400.11B (amino acid)	-
	Contains a transmembrane	
	domain	
485	LS #1043400.11A (amino acid)	-
486	LS #1043400.10 (amino acid)	-
487	LS #1043400.1 (amino acid)	-

nd=not determined

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Initially it appeared that these sequences represented overlapping and/or discrete sequences of O772P splice forms that were capable of encoding polypeptides unique to the specific splice forms of O772P. However, nucleotide alignment of these sequences failed to identify any identical regions within the repeat elements. This indicates that the sequences may represent different specific regions of a single O772P gene, one that contains 16 or more repeat domains, all of which form a single linear transcript. The 5'-end of sequence LS #1043400.10 (Table 2; SEQ ID NO:465) is unique to both O772P and FLJ14303 and contains no repeat elements, indicating that this sequence may represent the 5'-end of O772P.

Previously, transmembrane prediction analysis had indicated that O772P contained between 1 and 3 transmembrane spanning domains. This was verified by the

use of immunohistochemistry and flow cytometry, which demonstrated the existence of a plasma membrane-associated molecule representing O772P. However, immunohistochemistry also indicated the presence of secreted form(s) of O772P, possibly resulting from an alternative splice form of O772P or from a post-translational cleavage event. Analysis of several of the sequences presented in Table 2 showed that sequences 1043400B.12, 1043400.8B, and 1043400.11B all contained transmembrane regions, while 1043400.8A, 1043400.10, 1043400.1, 1043400.11A, and 1043400.9 were all lacking transmembrane sequences, suggesting that these proteins may be secreted.

Analysis indicates a part of O772P is expressed and/or retained on the plasma membrane, making O772P an attractive target for directing specific immunotherapies, e.g., therapeutic antibodies, against this protein. The predicted extracellular domain of O772P is disclosed in SEQ ID NO:489 and secretion of O772P is likely to occur as a result of a cleavage event within the sequence:

SLVEQVFLD<u>K</u>TLNASFHWLGSTYQLVDIHVTEMESSVYQP.

Proteolytic cleavage is most likely to occur at the Lysine (K) at position 10 of SEQ ID NO:489. The extracellular, transmembrane, and cytoplasmic regions of O772P are all disclosed in SEQ ID NO:488:

Extracellular:

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SLVEQVFLDKTLNASFHWLGSTYQLVDIHVTEMESSVYQPTSSSS
TQHFYLNFTITNLPYSQDKAQPGTTNYQRNKRNIEDALNQLFRNSSIKSYFSDCQ
VSTFRSVPNRHHTGVDSLCNFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDR
SSVLVDGYFPNRNEPLTGNSDLPF

Transmembrane:

WAVILIGLAGLLGLITCLICGVLVTT

Cytoplasmic:

RRRKKEGEYNVQQQCPGYYQSHLDLEDLQ

EXAMPLE 14

IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS OF O8E EXPRESSION IN OVARIAN CANCER AND NORMAL TISSUES

In order to determine which tissues express the ovarian cancer antigen O8E, IHC analysis was performed on a diverse range of tissue sections using both polyclonal and monoclonal antibodies specific for O8E. The generation of O8E specific polyclonal antibodies is described in detail in Example 8. The monoclonal antibodies used for staining were 11A6 and 14F1, both of which are specific for amino acids 61-80 of O8E and 18A8, which recognizes amino acids 151-170 of O8E (see Example 12 for details on generation).

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To perform staining, tissue samples were fixed in formalin solution for 12-24 hours and embedded in paraffin before being sliced into 8 micron sections. Steam heat induced epitope retrieval (SHEIR) in 0.1M sodium citrate buffer (pH 6.0) was used for optimal staining conditions. Sections were incubated with 10% serum/PBS for 5 minutes. Primary antibody was then added to each section for 25 minutes followed by 25 minutes of incubation with either anti-rabbit or anti-mouse biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 minute incubations with hydrogen peroxidase. The avidin biotin complex/horse radish peroxidase (ABC/HRP) system was used along with DAB chromogen to visualize the antigen expression. Slides were counterstained with hematoxylin to visualize the cell nuclei.

Results using rabbit affinity purified polyclonal antibody to O8E (a.a. 29-283; for details on the generation of this Ab, see Example 3) are presented in Table 3. Results using the three monoclonal antibodies are presented in Table 4.

<u>Table 3</u>
<u>Immunohistochemistry analysis of O8E using polyclonal antibodies</u>

Tissue	O8E Expression	
Ovarian Cancer	Positive	
Breast Cancer	Positive	

Normal Ovary	Positive	
Normal Breast	Positive	
Blood Vessel	Positive	
Kidney	Negative	
Lung	Negative	
Colon	Negative	
Liver	Negative	
Heart	Negative	

<u>Table 4</u>
<u>Immunohistochemistry analysis of O8E using monoclonal antibodies</u>

Normal	11A6		18A8		14F1	
Tissue	Endothelia	Epithelial	Endothelial	Epithelial	Endothelial	Epithelial
	1					
Skin	2	2	0	0	1	1
Skin	1	1	0	0	1	1
Breast	0	1	n/a	n/a	1	1
Colon	0	0	0	0	0	0
Jejunum	0	0	0	0	0	0
Colon	0	0	0	0	0	0
Colon	0	0	0	0	0	0
Ovary	0	0	0	0	1	0 .
Colon	0	0	0	0	0	1
Liver	0	0	0	0	1	2
Skin	0	0	0	0	1	0
Duodenum	0	0	0	0	0	0
and Pancreas				~ 		
Appendix	0	0	0	0	0	0
Ileum	0	0	0	0	0	0

0=no staining, 1=light staining, 2=moderate staining, n/a=not available

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EXAMPLE 15 EPITOPE MAPPING OF O772P POLYCLONAL ANTIBODIES

To perform epitope mapping of O772P, peptides were generated, the sequences of which were derived from the sequence of O772P. These peptides were 15 mers that overlapped by 5 amino acids and were generated via chemical synthesis on membrane supports. The peptides were covalently bound to Whatman 50 cellulose support by their C-terminus with the N-terminus unbound. In order to determine epitope specificity, the membranes were wet with 100% ethanol for 1 minute, and then blocked for 16 hours in TBS/Tween/Triton buffer (50mM Tris, 137 mM NaCl, 2.7 mM 10 KCl, 0.5% BSA, 0.05% Tween 20, 0.05% Triton X-100, pH 7.5). The peptides were then probed with 2 O772P specific antibodies, O772P-1 (amino acids 44-772 of SEQ ID NO:312) and O772P-2 (477-914 of SEQ ID NO:312; see Example 10 for details of antibody generation), as well as irrelevant rabbit antibodies for controls. The antibodies were diluted to lug/ml and incubated with the membranes for 2 hours at room 15 temperature. The membranes were then washed for 30 minutes in TBS/Tween/Triton buffer, prior to being incubated with a 1:10,000 dilution of HRP-conjugated anti-rabbit secondary antibody for 2 hours. The membranes were again washed for 30 minutes in TBS/Tween/Triton and anti-peptide reactivity was visualized using ECL. Specific epitope binding specificity for each of the O772P-polyclonal antibodies is described in Table 5. 20

Table 5

SEQ ID NO:	Peptide #	Anti-O772P1	Anti-O772P2	Peptide Sequence
490	2	***	-	TCGMRRTCSTLAPGS
491	6	*	*/-	CRLTLLRPEKDGTAT
492	7	*	-	DGTATGVDAICTHHP
493	8	-	•	CTHHPDPKSPRLDRE
494	9	***	***	RLDREQLYWELSQLT
495	11	*/-	•	LGPYALDNDSLFVNG
496	13	****	-	SVSTTSTPGTPTYVL
497	22	-	-	LRPEKDGEATGVDAI
498	24	**	*/-	DPTGPGLDREQLYLE
499	27	*/-	· -	LDRDSLYVNGFTHRS
500	40	*/-	-	GPYSLDKDSLYLNGY
501	41			YLNGYNEPGPDEPPT
502	47	***	***	ATFNSTEGVLQHLLR

503	50	•	***	QLISLRPEKDGAATG
504	51	-	**	GAATGVDTTCTYHPD
505	52	-	*/-	TYHPDPVGPGLDIQQ
506	53	-	*	LDIQQLYWELSQLTH
507	58	-	*	HIVNWNLSNPDPTSS
508	59	-	*	DPTSSEYITLLRDIQ
509	60	-	*	LRDIQDKVTTLYKGS
510	61	-	***	LYKGSQLHDTFRFCL
511	71	_	**	DKAQPGTTNYQRNKR

^{*=} relative reactive level, -; no binding, ****; maximal binding

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EXAMPLE 16 IDENTIFICATION OF A NOVEL N-TERMINAL REPEAT STRUCTURE ASSOCIATED WITH O772P

Various O772P cDNA and protein forms have been identified and characterized as detailed above (e.g., Examples 1, 2, 9, and 14). Importantly, O772P RNA and protein have been demonstrated to be over-expressed in ovarian cancer tissue relative to normal tissues and thus represents an attractive target for ovarian cancer diagnostic and therapeutic applications.

Using bioinformatic analysis of open reading frames (ORFs) from genomic nucleotide sequence identified previously as having homology with O772P, multiple nucleotide repeat sequences were identified in the 5' region of the gene encoding the O772P protein. A number of these repeat sequences were confirmed by RT-PCR using primers specific for the individual repeats. Fragments which contained multiple repeats were amplified from cDNA, thus confirming the presence of specific repeats and allowing an order of these repeats to be established.

Unexpectedly, when various sets of O772P sequences derived from different database and laboratory sources were analyzed, at least 20 different repeat structures, each having substantial levels of identity with each other (see Table 6), were identified in the 5' region of the O772P gene and the corresponding N-terminal region of the O772P protein. Each repeat comprises a contiguous open reading frame encoding a polypeptide unit that is capable of being spliced to one or more other repeats such that concatomers of the repeats are formed in differing numbers and orders. Interestingly, other molecules have been described in the scientific literature that have repeating structural domains analogous to those described herein for O772P. For example, the

mucin family of proteins, which are the major glycoprotein component of the mucous which coats the surfaces of cells lining the respiratory, digestive and urogenital tracts, have been shown to be composed of tandemly repeated sequences that vary in number, length and amino acid sequence from one mucin to another (Perez-Vilar and Hill, *J. Biol. Chem. 274(45)*:31751-31754, 1999).

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The various identified repeat structures set forth herein are expected to give rise to multiple forms of O772P, most likely by alternative splicing. The cDNA sequences of the identified repeats are set forth in SEQ ID NOs:513-540, 542-546, and 548-567. The encoded amino acid sequences of the repeats are set forth in SEQ ID NOs:574-593. In many instances these amino acid sequences represent consensus sequences that were derived from the alignment of more than one experimentally derived sequence.

Each of these splice forms is capable of encoding a unique O772P protein with multiple repeat domains attached to a constant carboxy terminal protein portion of O772P that contains a trans membrane region. The cDNA sequence of the O772P constant region is set forth in SEQ ID NO:568 and the encoded amino acid sequence is set forth in SEQ ID NO:594.

All of the available O772P sequences that were obtained were broken down into their identifiable repeats and these sequences were compared using the Clustal method with weighted residue weight table (MegAlign software within DNASTAR sequence analysis package) to identify the relationship between the repeat sequences. Using this information, the ordering data provided by the RT-PCR, and sequence alignments (automatic and manual) using SeqMan (DNASTAR), one illustrative consensus full length O772P contig was identified comprising 20 distinct repeat units. The cDNA for this O772P cDNA contig is set forth in SEQ ID NO:569 and the encoded amino acid sequence is set forth in SEQ ID NO:595. This form of the O772P protein includes the following consensus repeat structures in the following order:

SEQ ID NO:572- SEQ ID NO:574- SEQ ID NO:575-SEQ ID NO:576-30 SEQ ID NO:577- SEQ ID NO:578- SEQ ID NO:579- SEQ ID NO:580- SEQ ID NO:581- SEQ ID NO:582- SEQ ID NO:583- SEQ ID NO:584- SEQ ID NO:585- SEQ 10

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ID NO:586- SEQ ID NO:587- SEQ ID NO:588- SEQ ID NO:589- SEQ ID NO:590- SEQ ID NO:591- SEQ ID NO:592- SEQ ID NO:593.

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SEQ ID NO:595, therefore, represents one illustrative full-length consensus sequence for the O772P protein. As discussed above, however, based on current knowledge of this protein and based upon scientific literature describing proteins containing analogous repeating structures, many other forms of O772P are expected to exist with either more or less repeats. In addition, many forms of O772P are expected to have differing arrangements, e.g., different orders, of these N-terminal repeat structures. The existence of multiple forms of O772P having differing numbers of repeats is supported by Northern analysis of O772P. In this study, Northern hybridization of a O772P-specific probe resulted in a smear of multiple O772P-hybridizing transcripts, some in excess 10kb.

Thus, the variable repeat region of the O772 protein can be illustratively represented by the structure Xn – Y, wherein X comprises a repeat structure having at least 50% identity with the consensus repeat sequence set forth in SEQ ID NO:596; n is the number of repeats present in the protein and is expected to typically be a integer from 1 to about 35; Y comprise the O772P constant region sequence set forth in SEQ ID NO:594 or sequences having at least 80% identity with SEQ ID NO:594. Each X present in the Xn repeat region of the O772 molecule is different.

To determine the consensus sequences of each of the 20 repeat regions, sequences that were experimentally determined for a discrete repeat region were aligned and a consensus sequence determined. In addition to determining the consensus sequences for individual repeat regions, a consensus repeat sequence was also determined. This sequence was obtained by aligning the 20 individual consensus sequences. Variability of the repeats was determined by aligning the consensus amino acid sequences from each of the individual repeat regions with the over all repeat consensus sequence. Identity data is presented in Table 6.

<u>Table 6</u>

<u>Percent identities of Repeat Sequences with Reference to the Consensus Repeat Sequence</u>

Repeat Number	SEQ ID NO:	Percent Identity to
(amino acid)	Consensus Re	
		Sequence
2	574	88
3	575	84
4	. 576	88
5	577	89
6	578	93
7	579	90
8	580	91
9	581	88
10	582	85
11	583	86
12	. 584	87
13	585	87
14	586	89
15	587	89
16	588	89
17	589	83
18	590	84
19	591	83
20	592	57
21	593	68

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration,

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various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

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CLAIMS

What is Claimed:

1. An O772P polypeptide having the structure:

 X_n-Y

wherein X comprises a sequence having at least 50% identity with the consensus O772P repeat sequence set forth in SEQ ID NO: 596;

Y comprises a sequence having at least 80% identity with the O772P constant region sequence set forth in SEQ ID NO: 594;

n is an integer from 1 to 35;

wherein each X present in said polypeptide is different.

- 2. The polypeptide of claim 1, wherein X comprises a sequence selected from the group consisting of any one of SEQ ID NOs: 574-593.
- 3. The polypeptide of claim 1, wherein Y comprises the sequence set forth in SEQ ID NO: 594.
 - 4. The polypeptide of claim 1, wherein n is an integer from 15 to 25.
 - 5. The polypeptide of claim 1, wherein n is 20.
- 6. The polypeptide of claim 1, wherein said polypeptide comprises SEQ ID NO: 595.
- 7. The polypeptide of claim 1, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.
 - 8. An O772P polypeptide having the structure:

 X_n-Y

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wherein X comprises an O772P repeat sequence selected from the group consisting of any one of SEQ ID NOs: 574-593;

Y comprises a sequence having at least 90% identity with the O772P constant region sequence set forth in SEQ ID NO: 594;

n is an integer from 15 to 25;

wherein each X present in said polypeptide is different.

- 9. The polypeptide of claim 8, wherein n is 20.
- 10. The polypeptide of claim 8, wherein said polypeptide comprises SEQ ID NO: 595.
- 11. The polypeptide of claim 8, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.
 - 12. An O772P polypeptide having the structure:

 $X_{n}-Y$

wherein n is 20 and X comprises the following O772P repeat sequences:

SEQ ID NO: 574 - SEQ ID NO: 575 - SEQ ID NO: 576 - SEQ ID NO: 577 - SEQ ID NO: 578 - SEQ ID NO: 579 - SEQ ID NO: 580 - SEQ ID NO: 581 - SEQ ID NO: 582 - SEQ ID NO: 583 - SEQ ID NO: 584 - SEQ ID NO: 585 - SEQ ID NO: 586 - SEQ ID NO: 587 - SEQ ID NO: 588 - SEQ ID NO: 589 - SEQ ID NO: 590 - SEQ ID NO: 591 - SEQ ID NO: 592 - SEQ ID NO: 593; and

Y comprises the sequence set forth in SEQ ID NO: 594.

- 13. The polypeptide of claim 12, wherein said polypeptide comprises SEQ ID NO: 595.
- 14. The polypeptide of claim 12, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.

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15. An O772P polynucleotide having the structure:

 $X_{n}-Y$

wherein X comprises an O772P repeat sequence selected from the group consisting of any one of SEQ ID NOs: 512-540, 542-546 and 548-567;

Y comprises a sequence having at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 568;

n is an integer from 1 to 35;

wherein each X present in said polypeptide is different.

- 16. The polynucleotide of claim 15, wherein said polynucleotide comprises SEQ ID NO: 569.
 - 17. The polynucleotide of claim 15, wherein n is from 15 to 25.
 - 18. The polynucleotide of claim 15, wherein n is 20.
- 19. The polynucleotide of claim 15, wherein said polynucleotide is overexpressed in ovarian cancer cells compared with normal tissues.
- 20. An isolated polynucleotide comprising a sequence selected from the group consisting of:
 - (a) sequences provided in SEQ ID NOs: 464-477 and 512-569;
- (b) complements of the sequences provided in SEQ ID NOs: 464-477 and 512-569;
- (c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NOs: 464-477 and 512-569;
- (d) sequences that hybridize to a sequence provided in SEQ ID NOs: 464-477 and 512-569, under highly stringent conditions;
- (e) sequences having at least 75% identity to a sequence of SEQ ID NOs: 464-477 and 512-569;

- (f) sequences having at least 90% identity to a sequence of SEQ ID NOs: 464-477 and 512-569; and
- (g) degenerate variants of a sequence provided in SEQ ID NOs: 464-477 and 512-569.
- 21. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:
 - (a) sequences encoded by a polynucleotide of claim 20; and
- (b) sequences having at least 80% identity to a sequence encoded by a polynucleotide of claim 20; and
- (c) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 20.
- 22. An expression vector comprising a polynucleotide of claim 20 operably linked to an expression control sequence.
- 23. A host cell transformed or transfected with an expression vector according to claim 22.
- 24. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 21.
- 25. A method for detecting the presence of a cancer in a patient, comprising the steps of:
 - (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 21;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

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- 26. A fusion protein comprising at least one polypeptide according to claim 21.
- 27. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:
 - (a) polypeptides according to claim 21;
 - (b) polynucleotides according to claim 20; and
- (c) antigen-presenting cells that express a polynucleotide according to claim 20,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 28. An isolated T cell population, comprising T cells prepared according to the method of claim 27.
- 29. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:
 - (a) polypeptides according to claim 21;
 - (b) polynucleotides according to claim 20;
 - (c) antibodies according to claim 24;
 - (d) fusion proteins according to claim 26;
 - (e) T cell populations according to claim 28; and
- (f) antigen presenting cells that express a polypeptide according to claim 21.
- 30. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 29.

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- 31. A method for the treatment of a ovarian cancer in a patient, comprising administering to the patient a composition of claim 29.
- 32. A method for determining the presence of a cancer in a patient, comprising the steps of:
 - (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide that hybridizes to a polynucelotide sequence according to claim 21 under moderately stringent conditions;
- (c) detecting in the sample an amount of said polynucleotide that hybridizes to the oligonucleotide; and
- (d) comparing the amount of said polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.
- 33. An O772 polypeptide comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 490-511.
- 34. An O8E polypeptide comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 394-415.
- 35. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 1.

1/101

11729.1 contg

11729-45.21.21.cons1

11729-45.21.21.cons2

11731.1contig

TCTTTTCTTTCGATTTCCTTCAATTTGTCACGTTTGATTTTATGAAGTTGTTCAAGGGCTAACTGCTGTGTAT
TATAGCTTTCTCTGAGTTCCTTCAGCTGATTGTTAAATGAATCCATTTCTGAGAGCCTTAGATGCAGTTTCTTTT
TCAAGAGCATCTAATTGTTCTTTAAGTCTTTTGGCATAATTCTTTCCTTTTCTGATGACTTTTTATGAAGTAAACT
GATCCCTGAATCAGGTGTGTTACTGAGCTGCATGTTTTTAATTCTTTCGTTTAATAGCTGCTTCTCAGGGACCA
GATAGATAAGCTTATTTTGATATTCCTTAAGCTCTTGTTGAAGTTGTTTGATTTCCATAATTTCCAGGTCACAC
TGTTTATCCAAAACTTCTAGCTCAGTCTTTTGTGTTTGCTTTCTGATTTGGACATCTTGTAGTCTGCCTGAGAT
CTGCTGATGXTTTCCATTCACTGCTTCCAGTTCCAGGTGGAGACTTTXCTTTCTGGAGCTCAGCCTGACAATGC
CTTCTTGXTCCCT

Fig. 1A

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11731.2contig

11734.1contig

11734.2contig

GCCAAGAAAGCCCGAAAGGTGAAGCATCTGGATGGGGAAGAGGATGGCAGCAGTGATCAGAGTCAGGCTTCTGG
AACCACAGGTGGCCGAAGGGTCTCAAAGGCCCTAATGGCCTCAATGGCCCGCAGGGCTTCAAGGGGTCCCATAG
CCTTTTGGGCCCGCAGGGCATCAAGGACTCGGTTGGCTGCTTGGGCCCGGAGAGCCTTGCTCTCCCTGAGATCA
CCTAAAGCCCGTAGGGGCAAGGCTCGCCGTAGAGCTGCCAAGCTCCAGTCATCCCAAGAGCCTGAAGCACCACC
ACCTCGGGATGTGGCCCTTTTGCAAGGGAGGGCAAATGATTTGGTGAAGTACCTTTTTGGCTAAAGACCAGACGA
AGATTCCCATCAAGCGCTCGGACATGCTGAAGGACATCATCAAAGAATACACTGATGTGTACCCCGAAATCATT
GAACGAGCAGGCTATTCCTTGGAGAAAGGTATTTGGGATTCAATTGAAGGAAATTGATAAGAATGACCACTTGTA
CATTCTTCTCAGC

11736.1contg

3/101 11736.2contig

11739-1&2

11740.1.contig

Fig. 1C

4/101

11766.1.contig

11766.2.contig

11773.2.contig

11775-1&2

5/101 11777.1&2.cons

11779.2.contig

11781 & 37.cons

6/101 11781-76-87-37

11784-1 & 2

11785.2.contig

7/101 11718-1&2 cons

13690.4

CAACTTATTACTTGAAATTATAATATAGCCTGTCCGTTTGCTGTTTCCAGGCTGTGATATATTTTCCTAGTGGT TTGACTTTAAAAATAAAGGTTTAATTTTCTCCCC

13693.1

13694.1

Fig. 1G

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13694.2

GACTGTCCTGAACAAGGGACCTCTGACCAGAGAGCTGCAGGAGATGCAGAGTGGCAGGAGTGGAAGCCAAA
GAACACCCACCTTCCTCCCTTGAAGGAGTAGAGCAACCCACCATCAGAAGATACTGTTTTATTGCTCTGGTCAAACAA
GTCTTCCTGAGTTGACAAAACCTCAGGCTCTGGTGACTTCTGAATCTGCAGTCCACTTTCCATAAGTTCTTGTG
CAGACAACTGTTCTTTTGCTTCCATAGCAGCAACAGATGCTTTGGGGCTAAAAAGGCATGTCCTCTGACCTTGCA
GGTGGTGGATTTTGCTCTTTTACAACATGTACATCCTTACTGGGCTGTGCTGTCACAGGGATGTCCTTGCTGGA
CTGTTCTGCTATGGGGATATCTTCGTTGGACTGTTCTTCATGCTTAATTGCAGTATTAGCATCCACATCAGACA
GCCTGGTATAACCAGAGTTGGTGGTTACTGATTGTAGCTGCTCTTTTGTCCACTTCATATGGCACAAAGTATTTTC
CTCAACATCCTGGCTCTGGGAAG

13695.1

GAAATGTATATTTAATCATTCTCTTGAACGATCAGAACTCTRAAATCAGTTTTCTATAACARCATGTAATACAG
TCACCGTGGCTCCAAGGTCCAGGAAGGCAGTGGTTAACACATGAAGAGTGTGGGAAGGGGGCTGGAAACAAAGT
ATTCTTTTCCTTCAAAGCTTCATTCCTCAAGGCCTCAATTCAAGCAGTCATTGTCCTTGCTTTCAAAAGTCTGT
GTGTGCTTCATGGAAGGTATATGTTTGTTGCCTTAATTTGAATTGTGGCCAGGAAGGGTCTGGAGATCTAAATT
CAGAGTAAGAAACCTGAGCTAGAACTCAGGCATTTCTCTTTACAGAACTTGGCTTGCAGGGTAGAATGAANGGA
AAGAAACTTAGAAGCTCAACAAGCTGAAGATAATCCCATCAGGCATTTCCCATAGGCCTTGCAACTCTGTTCAC
TGAGAGATGTTATCCTG

13695.2

13697.1

TAGCTGTCTTCCTCACTCTTATGGCAATGACCCCCATATCTTAATGGATTAAGATAATGAAAGTGTATTTCTTAC ACTCTGTATCTATCACCAGAAGCTGAGGTGATAGCCCGCTTGTCATTGTCATCCATATTCTGGGACTCAGGCGG GAACTTTCTGGAATATTGCCAGGGAGCATGGCAGAGGGGCACAGTGCATTCTGGGGAATGCACATTGGCTCAG CCTGGGTAATGAGTGATATACATTACCTCTGTTCACAACTCATTGCCCAGCACCAGACCCAAATCCCAAGACCCCAAATGTAGTCCTGTTGATATGGTTTTGCTGTGTCCCAACCCAAATCTCATCTTGAATTGT AAGCTCCCATAATTCCCATGTGTTGTGGGAGGGACCTGGTG

Fig. 1H

9/101

13697.2

13699.182

13703.3

13705.1

Fig. 11

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13705.2

13707.4

13708.182

GGCGGGTAGGCATGGAACTGAGAAGAACGAAGAAGCTTTCAGACTACGTGGGGAAGAATGAAAAAACCAAAATT
ATCGCCAAGATTCAGCAAAGGGGACAGGGAGCTCCAGCCCGAGAGCCTATTATTAGCAGTGAGGAGCAGAAGCA
GCTGATGCTGTACTATCACAGAAGACAAGAGGAGCTCAAGAGATTGGAAGAAAATGATGATGATGCCTATTTAA
ACTCACCATGGGCGGATAACACTGCTTTGAAAAGACATTTTCATGGAGTGAAAGACATAAAGTGGAGACCAAGA
TGAAGTTCACCAGCTGATGACACTTCCAAAGAGATTAGCTCACCT

13709.1

11/101 13709.2

TATGAAGAAGGGAAAAGAAGATAATTTGTGAAAGAAATGGGTCCAGTTACTAGTCTTTGAAAAGGGTCAGTCTG
TAGCTCTTCTTAATGAGAATAGGCAGCTTTCAGTTGCTCAGGGTCAGATTTCCTTAGTGGTGTATCTAATCACA
GGAAACATCTGTGGTTCCCTCCAGTCTCTTTCTGGGGGGACTTGGGCCCACTTCTCATTTCATTTAATTAGAGGA
AATAGAACTCAAAGTACAATTTACTGTTGTTTAACAATGCCACAAAGACATGGTTGGGAGCTATTTCTTGATTT
GTGTAAAATGCTGTTTTTGTGTGCTCATAATGGTTCCAAAAAATTGGGTGCTGGCCAAAGAGAGATACTGTTACA
GAAGCCAGCAAGAAGACCTCTGTTCATTCACACCCCCCGGGGATATCAGGAATTGACTCCAGTGTGTGCAAATCC
AGTTTGGCCTATCTTCT

13712.1&2

13714.1&2

13716.1&2

Fig. 1K

12/101

13718.2

13722.3

CATGCGTTTCACCACTGTTGGCCAGGCTGGTCTCGAACTCCTGGCCTCAAGCAATCCACCCGCCTCAGCCTCCA
AAAGTGCTGGGATTACAGATGTGAGCCATGGCACCATGCCAAAAGGCTATATTCCTGGCTCTGTGTTTCCGAGA
CTGCTTTTAATCCCAACTTCTCTACATTTAGATTAAAAAAATATTTTATTCATGGTCAATCTGGAACATAATTAC
TGCATCTTAAGTTTCCACTGATGTATATAGAAGGCTAAAGGCACAATTTTTATCAAATCTAGTAGAGTAACCAA
ACATAAAATCATTAATTACTTTCAACTTAATAACTAATTGACATTCCTCAAAAGAGCTGTTTTCAATCCTGATA
GGTTCTTTATTTTTTCAAAATATATTTGCCATGGGATGCTAATTTGCAATAAGGCGCATAATGAGAATACCCCA
AACTGGA

13722.4

13724-13698-13748

Fig. 1L

13/101

13730.1

13732.1

ATGGATCTTACTTTGCCACCCAGGTTGGAGTGCAGTGCTGCAATCTTGGCTCACTGCAGCCTTAACCTCCCAGG CTCAAGCTATCCTCCTGCCAAAGCCTTCCACATAGCTGGGACTACAGGTACACNGCCACCACACCCAGCTAAAA TTTTTGTATTTTTTGTAGAGACGGGATCTCGCCACGTTGCCCAGGCTGGTCCCATCCTGACCTCAAGCAGATCT GCCCACCTCAGCCCCCCAACGTGCTAGGATTACAGGCGTGAGCCACCCGCACCCAGCCTTTGTTTTGCTTTTAAT GGAATCACCAGTTCCCCTCCGTGTCTCAGCAGCAGCTGTGAGAAATGCTTTGCATCTGTGACCTTTATGAAGGG GAACTTCCATGCTGAATGAGGGTAGGATTACATGCTCCTGTTTTCCCGGGGGGTCAAGAAAGCCTCAGACTCCAGC ATGATAAGCAGGGTGAG

13732.2

Fig. 1M

14/101

13735.1

13735.2

13736.1

13737.182

Fig. 1N

15/101 13738.1

TTTGACTTTAGTAGGGGTCTGAACTATTTATTTTACTTTGCCMGTAATATTTARACCYTATATATCTTTCATTA
TGCCATCTTATCTTCTAATGBCAAGGGAACAGWTGCTAAMCTGGCTTCTGCATTWATCACATTAAAAATGGCTT
TCTTGGAAAATCTTCTTGATATGAATAAAGGATCTTTTAVAGCCATCATTTAAAGCMGGNTTCTCCCAACACG
AGTCTGCTSASGGGGGGKGAGCTGTGAACTCTGGCTGAAGGCTTTCCCATACACACTGCAATGACMTGGTTTCT
GACCAGBGTGAGTTA

13738.2

13739.182

GAGACAGGGTCTCACTTTGTCACCCAGGCTGGAATGCAGTGGTGCGATCTTACGTAGCTCACTGCAGCCCTGAC
CTCCTGGACTCAAACAATTCTCCTGCCTCAGCCCTGCAAGTAGCTGGGACTGTGGGTGCATGCCACCATGCCTG
GCTAACTTTTGTAGTTTTTTGTAAAGATGGGGTTTTGCCATGTTGCACATGCTGGTCTTGAACTCCTGAGCTCAA
ACGATCTGCCCACCTCGGCCTCCCAGAATGTTGGGATTACAGGGGTAAACCACCACGCCTGGCCCCATTAGGGT
ATTCTTAGCATCCACTTGCTCACTGAGATTAATCATAAGAGATGATAAGCACTGGAAGAAAAAAATTTTTACTA
GGCTTTGGATATTTTTTTCCTTTTTCAGCTTTATACAGAGAGTTGGATCTTTAGTTTTCCTTTAACTGATAATA
AAACATTGAAAGGAAATAAGTTTACCTGAGATTCACAGAGATAACCGGCATCACTCCCTTGCTCAATTCCAGTC
TTTACCACATCAATTATTTTCAGAGGTGCAGGATAAAGGCCTTTAGTCTGCTTTTCCACTTT
TTTGTAAACCTGTTGCCTGACAAATGGAATTGACAGCGTATGCCATGACTATTCCATTTTCTCCACTGT
TCAATTTTTCCACCAATCCCTTGTCTCTCTTTTGGAGAGAGTCTTCTTTATCAGCTAGTCCTTTTGGCAAAAGTAATT
GCAACTTCTTCTAGGTATTCTATTGTCCGTTCCACTGGTGGAACCCCTGGGACCAGGACTAAAACCTCCAG

13741.1

Fig. 10

16/101

13742.1

14351.1

14351.2

ACCTTAAAGACATAGGAGAATTTATACTGGGAGAGAAAGCTTACAAATGTAAGGTTTCTGACAAGACTTGGGAG TGATTCACACCTGGAACAACATACTGGACTTCACACTGGABAGAAACCTTACAAGTGTAATGAGTGTGGCAAAG CCTTTGGCAAGCAGTCAACACTTATTCACCATCAGGCAATTCA

14354.2

AGTCAGGATCATGATGGCTCAGTTTCCCACAGCGATGAATGGAGGGCCAAATATGTGGGCTATTACATCTGAAG
AACGTACTAAGCATGATAAACAGTTTGATAACCTCAAACCTTCAGGAGGTTACATAACAGGTGATCAAGCCCGT
ACTTTTTTCCTACAGTCAGGTCTGCCGGCCCCGGTTTTAGCTGAAATATGGGCCTTATCAGATCTGAACAAGGA
TGGGAAGATGGACCAGCAAGAGTTCTCTATAGCTATGAAACTCATCAAGTTAAAGTTGCAGGGCCAACAGCTGC
CTGTAGTCCTCCCTCCTATCATGAAACAACCCCCTATGTTCTCCCACTAATCTCTGCTCGTTTTTGGGATGGGA
AGCATGCCCAATCTGTCCATTCATCAGCCATTGCCTCCAGTTGCACCTATAGCAACACCCTTGTCTTCTGCTAC
TTCAGGGACCAGTATTCCTCCCTAATGATGCCTGCT

14354.1

Fig. 1P

17/101 16431.1.2

GTGGAGGTGAAACGGAGGCAAGAAAGGGGGCTACCTCAGGAGCGAGGGACAAAGGGGGCCGTGAGGCACCTAGGC
CGCGGCACCCCGGCGACAGGAAGCCGTCCTGAACCGGGCTACCGGGTAGGGGAAGGGCCCGCGTAGTCCTCGCA
GGGCCCCAGAGCTGGAGTCGGCTCCACAGCCCCGGGCCGTTCTCCACTTCCTGGACCTCCCCGGCGCCCG
GGCCTGAGGACTGGCTCGGCGGAGGGAGAAGAGGAAACAGACTTGAGCAGCTCCCCGTTGTCTCGCAACTCCAC
TGCCGAGGAACTCTCATTTCTTCCCTCGCTCCTTCACCCCCCCACCTCATGTAGAAAGGTGCTGAAGCGTCCGGA
GGGAAGAAGAACCTGGGCTACCGTCCTGGCCTTCCCMCCCCCTTCCCGGGGCGCTTTGGTGGGCGTGGAGTTGG
GGTTGGGGGGGTGGGTGGGGGTTCTTTTTTTGGAGTGCTGGGGAACTTTTTTCCCTTCTTCAGGTCAGGGAAAG
GGAATGCCCAATTCAGAGAGACATGGGGGCAAGAAGGACGGGAAGTGGAGGAGCTTCTGGAACTTTGCAGCCGTC
ATCGGGAGGCGGCAGCTCTAACAGCAGAGAGCGTCACCGCTTGGTATCGAAGCACAAGCGGCATAAGTCCAAAC
ACTCCAAAGACATGGGGTTGGTGACCCCCCGAAGCAGCATCCCTGGGCACAGTTATCAAACCTTTTGGTGGAGTAT
GATGATATCAGCTCTGATTCCGACACCTTCTCCCGATGACATCGTCACCACCAGCACAGGCGTTCCCGGGACTTAC
TAAAAGCTAAACAGACCG

16432-1

16432-2

17184.3

Fig. 1Q

18/101 17184.4

CAAGCGTTCCTTTATGGATGTAAATTCAAACAGTCATGCTGAGCCATCCCGGGCTGACAGTCACGTTWAAGACA CTAGGTCGGGCGCCACAGTGCCACCCAAGGAGAAGAAGAATTTTGGAATTTTTCCATGAAGATGTACGGAAATCT GATGTTGAATATGAAAATGGCCCCCAAATGGAATTCCAAAAGGTTACCACAGGGGCTGTAAGACCTAGTGACCC TCCTAAGTGGGAAAGAGGAATGGAGAATAGTATTTCTGATGCATCAAGAACATCAGAATATAAAACTGAGATCA TAATGAAGGAAAATTCCATATCCAATATGAGTTTACTCAGAGACAGTAGAAACTATTCCCAGG

17185.1

TAGGAATAACAAATGTTTATTCAGAAATGGATAAGTAATACATAATCACCCTTCATCTCTTAATGCCCCTTCCT
CTCCTTCTGCACAGGAGACACAGATGGGTAACATAGAGGCATGGGAAGTGGAGGAGGACACAGGACTAGCCCAC
CACCTTCTCTCTCCCGGTCTCCCCAAGATGACTGCTTATAGAGTGGAGGAGGCAAACAGGTCCCCTCAATGTACCA
GATGGTCACCTATAGCACCAGCTCCAGATGGCCACGTGGTTGCAGCTCGACTCAATGAAACTCTGTGACAACCA
GAAGATACCTGCTTTGGGATGAGAGGGAGGATAAAGCCATGCAGGAGGATATTTACCATCCCTACCCTAAGCA
CAGTGCAAGCAGTGAGCCCCCGGCTCCCAGTACCTGAAAAACCAAGGCCTACTGNCTTTTGGATGCTCTCTTGG
GCCACG

17188.2

17190.1

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17190.2

17191.2889.2

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AGCCAGATGGCTGAGAGCTGCAAGAAGAAGTCAGGATCATGATGGCTCAGTTTCCCACAGCGATGAATGGAGGG CCAAATATGTGGGCTATTACATCTGAAGAACGTACTAAGCATGATAAACAGTTTGATAACCTCAAACCTTCAGG AGGTTACATAACAGGTGATCAAGCCCGTACTTTTTTCCTACAGTCAGGTCTGCCGGCCCCGGTTTTAGCTGAAA TATGGGCCTTATCAGATCTGAACAAGGATGGGAAGATGGACCAGCAAGAGTTCTCTATAGCTATGAAACTCATC ACTAATCTCTGCTCGTTTTGGGATGGGAAGCATGCCCAATCTGTCCATTCATCAGCCATTGCCTCCAGTTGCAC CTATAGCAACACCCTTGTCTTCTGCTACTTCAGGGACCAGTATTCCTCCCCTAATGATGCCTGCTCCCCTAGTG CCTTCTGTTAGTACATCCTCATTACCAAATGGAACTGCCAGTCTCATTCAGCCTTTATCCATTCCTTC TTCAACATTGCCTCATGCATCATCTTACAGCCTGATGATGGGAGGATTTGGTGGTGCTAGTATCCAGAAGGCCC AGTCTCTGATTGATTTAGGATCTAGTAGCTCAACTTCCTCAACTGCTTCCCTCTCAGGGAACTCACCTAAGACA GGGACCTCAGAGTGGGCAGTTCCTCAGCCTTCAAGATTAAAGTATCGGCAAAAAATTTAATAGTCTAGACAAAGG CTACTATTTGGACTCTGGCTGACATCGATGGTGACGGACAGTTGAAAGCTGAAGAATTTATTCTGGCGATGCAC CTCACTGACATGGCCAAAGCTGGACAGCCACTACCACTGACGTTGCCCCCGAGCTTGTCCCTCCATCTTTCAG AGGGGGAAAGCAAGTTGATTCTGTTAATGGAACTCTGCCTTCATATCAGAAAACACAAGAAGAAGAAGACCCCAGA AGAAACTGCCAGTTACTTTTGAGGACAAACGGAAAGCCAACTATGAACGAGGAAACATGGAGCTGGAGAAGCGA GAAACAGAGAACTGCAAGAGCAAGAATGGAAGAAGCAGCTGGAGTTGGAGAAACGCTTGGAGAAACAGAGAG CATTGTCAGGCTGAGCTCCAGAAAGAAAAGTCTCCACCTGGAACTGGAAGCAGTGAATGGAAAACATCAGCAGA TCTCAGGCAGACTACAAGATGTCCAAATCAGAAAGCAAAACACAAAAGACTGAGCTAGAAGTTTTGGATAAACAG GGTCCCTGAGAAGCAGCTATTAAACGAAAGAATTAAAAACATGCAGCTCAGTAACACCCTGATTCAGGGATCA GTTTACTTCATAAAAAGTCATCAGAAAAGGAAGAATTATGCCAAAGACTTAAAGAACAATTAGATGCTCTTGAA AAAGAAACTGCATCTAAGCTCTCAGAAATGGATTCATTTAACAATCAGCTGAAGGAACTCAGAGAAAGCTATAA TAGAGCAAAAAAAAAAAA

21/101

ATGGCAGTGACATTCACCATCATGGGAACCACCTTCCCTTTTCTTCAGGATTCTCTGTAGTGGAAGAGAGCACC CAGTGTTGGGCTGAAAACATCTGAAAGTAGGGAGAAGAACCTAAAATAATCAGTATCTCAGAGGGCTCTAAGGT GCCAAGAAGTCTCACTGGACATTTAAGTGCCAACAAAGGCATACTTTCGGAATCGCCAAGTCAAAACTTTCTAA CTTCTGTCTCTCTCAGAGACAAGTGAGACTCAAGAGTCTACTGCTTTAGTGGCAACTACAGAAAACTGGTGTTA CCCAGAAAAACAGGAGCAATTAGAAATGGTTCCAATATTTCAAAGCTCCGCAAACAGGATGTGCTTTCCTTTTGC CCATTTAGGGTTTCTTCTTTTATTAACCACTA

22/101

ATATCTAGAAGTCTGGAGTGAGCAAACAAGAGCAAGAACAAAAAGAAGCCAAAAGCAGAAGGCTCCAATATGA ACAAGATAAATCTATCTTCAAAGACATATTAGAAGTTGGGAAAATAATTCATGTGAACTAGACAAGTGTGTTAA GGAGTGAGAGGACAGGATAGTGCATGTTCTTTGTCTCTGAATTTTTAGTTATATGTGCTGTAATGTTGCTCTGA GGAAGCCCCTGGAAAGTCTATCCCAACATATCCACATCTTATATTCCACAAATTAAGCTGTAGTATGTACCCTA AGACGCTGCTAATTGACTGCCACTTCGCAACTCAGGGGCGGCTGCATTTTAGTAATGGGTCAAATGATTCACTT TTTATGATGCTTCCAAAGGTGCCTTGGCTTCTCTCCCAACTGACAAATGCCAAAGTTGAGAAAAATGATCATA ATGCGGGTTTATTTCTCAGATGATGTTCATCCGTGAATGGTCCAGGGAAGGACCTTTCACCTTGACTATATGGC ATTATGTCATCACAAGCTCTGAGGCTTCTCCTTTCCATCCTGCGTGGACAGCTAAGACCTCAGTTTTCAATAGC ATCTAGAGCAGTGGGACTCAGCTGGGGTGATTTCGCCCCCCATCTCCGGGGGAATGTCTGAAGACAATTTTGTT ACCTCAATGAGGGAGTGGAGGATACAGTGCTACTACCAACTAGTGGATAAAGGCCAGGGATGCTGCTCAAC CTCCTACCATGTACAGGACGTCTCCCCATTACAACTACCCAATCCGAAGTGTCAACTGTGTCAGGACTAAGAAA GGCAAATAAGCATTCTGTCTCTTTGGCTGCCTCAGCACAGAGAGCCAGAACTCTATCGGGCACCAGGATAA CATCTCTCAGTGAACAGAGTTGACAAGGCCTATGGGAAATGCCTGATGGGATTATCTTCAGCTTGTTGAGCTTC TAAGTTTCTTTCCCTTCATTCTACCCTGCAAGCCAAGTTCTGTAAGAGAAATGCCTGAGTTCTAGCTCAGGTTT TGAAGCACACACAGACTTTTGAAAGCAAGGACAATGACTGCTTGAATTGAGGCCTTGAGGAATGAAGCTTTGAA GGAAAAGAATACTTTGTTTCCAGCCCCCTTCCCACACTCTTCATGTGTTAACCACTGCCTTCCTGGACCTTGGA GCCACGGTGACTGTATTACATGTTGTTATAGAAAACTGATTTTAGAGTTCTGATCGTTCAAGAGAATGATTAAA TATACATTTCCTA

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	Profess	1430	302	707	4180	818	483	743	129	627	5 85	365	573	199	1335	502	1256	1029	1449	1531	1278	883
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	8/8	13.3	2.7	6.9	445	3.8	14.8	3.5	10.6	3.3	:2:	7.5	3.4	4.5	8.4	22.	14.7	3.4	35.E	3.2	3.2	22.5
	Prober 8.19 4.2 Probe 2	2393	365	1298	0656	.516	2305	.631	1842	£3	1882	1488	936	7007	828	3836	2251	552	87.18	439	286	4242
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	ivite	19B (198) 96 K	71980) 98 K	198 (7.68	198 (4	1961	9810	136 (H96 (()196 (719B (4	H96 (M 9B (4) 98 ()) 86 1	138 (()) 961	198 (
	Franchin	[424 GD198 (C-11]	42100138[C11	42160196 (C-11	42100198 (C.11,	42160186 (C11;	क्यकाञ्च (८११)	42100188 [C11.	42100198 (CHT) 1842	424 50196 (5.11)	421 GO1486 (C;11;	42160186 (C11	421 G0196 (C:11)	421.00136 (C11.)	42160198 (C.11.)	42100196 (C11.)	421GD19B (C.11.	42100198 (C,11;	42/00/se (C11	42/150/36 (C:11	42100136 (C11	421G0198 (C-11
		ର	ត្ត	g	6	0	30)	g	8	6	e E	Ö.	(0)	íg.	Ŕ	(02	Q	S.	8	8	a	a
	GEM/Elagueri	(1) (1)	2B (45	3H (4)	23 (4)	05 (42	24 (4.	19 (43	09 (42	27 (42	302 (4	7) (7.	04 (42	35 (4,	520 (4	28 (4)	306 (4.	Ω (4)	07 (42	23 (42	10 (42	83 (42)
	GEM	42240808 (420)	42220628 (420)	42230621 (420)	422ND828 (430)	422,0605 (420)	42200624 (420)	422HD619 (420)	422E0609 (420)	42290627 (420)	42270602 (420)	42240622 (420)	422C0604 (420)	422Y0625 (420)	4224/0620 (420)	42200628 (420)	42200606 (420)	422R0801 (420)	422XD607 (420)	422)-10623 (420)	42200610 (420)	42250503 (420)
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	2	800		aresc	×	ctivate		rrow			(CD)	festin	estine		7	Nor			. 93			
	Pinte 2	erdia	N V	eletai	creas	9 2 8	N.	용	ż	Iriey N	15.P (arge t	nafi irt	N BUN	Stematch N	inal C	ver N		lai tiss	Sast N	rain N	Z X
		272A Dendrillo cells	ST-OVBRY N	SID Skeletal muscle N	S2 Pancreas N	S40 PBMC (activated)	CTS Heart N	CT4 Bone Marrow N	'II Colon N	CT9 Kidney N	9485 OT 5.P (SCID)	334A, Large Integline N	CT10 Small Intestine N	- GT12 Lung N	\$6 Sta	SS6 Spinal Cord N	270A.Liver N	N CINC	S91 Fetaltisaue	S73 Breast N	CT19 Brain N	S27 Ovary N
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Flement Display		384A Over	335A. Over	261A Ove	-284A Over	386A Over	2654-Over	S25 Overy	383A Over)	SZZ Ovary	9485 OT 1	262A Over	S115 Overy	ZBBA OVBI	201A Ovar	\$23 Overy	205A Ovan	9334 Overy	385A Overy	283A Ovar	382A Overy	286A Overy
Flem	Official	- 1	1.1	÷	+8.1	127	14.7	÷.		-1.9	+32	£ 1.5	1.1	1.11	-2.1	+7.B	₽.+	-1.9	9.5	3.5	33	+4B
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Fig. 7A

AGCGTGGTCGCGGCCGAGGTCCAGTCGCAGCATGCTCTTTCTCCTGCCCACTGGCACAGTGAGGAAGATCTCTG CTGTCAGTGAGAAGGCTGTCATCCACTGAGATGGCAGTCAAAAGTGCATTTAATACACCTAACGTATCGAACAT CATAGCTTGGCCCAGGTTATCTCATATGTGCTCAGAACACTTACAATAGCCTGCAGACCTGCCCGGGCGGCCGC TCGA

Fig. 7B

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TGTGGTGTTGAACTTCCTGGAGNCAGGGTGACCCATGTCCTCCCCATACTGCAGGTTGGTGATGGTGAAGTTGAGGGTGAATGGTTGACCAGGAGAGGGCCAGCAGCCATAATTGTSGRGCKGSMGMSSGAGGMWGGWGTYYCWGAGGTTCYRARRTCCACTGTGGAGGTCCCAGGAGTGCTGGTGGTGGGCACAGAGSTCYGATGGGTGAAACCATTGACATAGAGACTGTTCCTGTCCAGGGTGTAGGGGCCCAGCTCTTYRATGYCATTGGYCAGTTKGCTYAGCTCCCAGTACAGCCRCTCTCKGYYGMGWCCAGSGCTTTTGGGGTCAAGATGATGCAGATGCAGATGCATCCACTCCAGTGGCTGCTCCATCCTTCTCGGACCTGAGAGAGGGCCAACACTGGTGTTCTTTGAATA

29/101

TCGAGCGGCCGGGCAGGTCAGGAAGCACATTGGTCTTAGAGCCACTGCCTCCTGGATTCCACCTGTGCTGCGACATCTCCAGGGGAGTGCAGAAGCAGGGAAGCAGGTCAAACTGCTCAGATCAGACTAGACTAGCCTGCAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAGCCAGAACCCTGCTGCAGAACCCTCTTCCGTGGTGTTTGAACTTCCTGGAAACCAGGGTGTTGCATGTTTTTCCTCATAATGCAAGGTTGGTGATGG

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Prob62	8/8	22	35	20 20 20 20 20 20 20 20 20 20 20 20 20	7.6	4.5	2.6	2.1,	23	5.6	2.9	27.	*	30	9.5	60	26	4.0	7,	0.4	돐	653	5	85 85	
	7%	•		•					. ·	.⊶					:.·*	÷.			: .						٠.,
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Ä	8/B			_				•	25.0		٠,		٠.		٠.	٠.	٠.				•		•		٠.
Probe2	Value	1240	200	2121	1480	21.16	1113	8	131	3596	1081	26	964	817	\$ 1 \$ 2 \$ 2 \$ 2 \$ 3 \$ 3 \$ 4 \$ 4 \$ 4 \$ 4 \$ 4 \$ 4 \$ 4 \$ 4 \$ 4 \$ 4	3653	12.23	1072.	3074	2101	1297	708	1663	1473	1204
Probai	Value	8620	283 5	12151	7487	7302	37.14	2535	4578	2005	2191	6661	<u>16</u>	1666	183	2914	2039	1736	4204	3000	1643	252	2072	1840	1329
GEM	Ü	42200606	N 422GU628	422X0607	422X0611	422HD623	422B0609	422R0601	11,422,40608	422ND629	rat42210605	dn422C0604	42200624	42220626	N42240612	SH42230621	42250603	42290627	ID422X0602	hr422A0622	w 422H0619	42210614	42200610	422V0625	4225V0620
Probe 2	Name	270A Liver N	SS6 Spinal Cord	S91. Fetal tissue.	415A Aorta N	S73 Breast'N	11 Colon N	12 Skin N	272A Dendritie e	S2 Pancreas N	S40 PBMC facti	CT10 Small intes	CTS Heart N	S7 Ovary N	243A Esquingus	\$10. Skeletal mu	SZZ Ovary N	C'TO Kidney N	9485 OT S.P. CC	334A Large Inter	CT4 Bone Marro	364'x Ovary'N	CT19 Brain N	CT12 Ling N	S6 Stornach N.
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Bal Probe 1	Exp. Name	4:7.0 205A Ovary T	#5.9.523 Ovary T	+5.7 385A Overy T		43.5 263A Ovary T		+3.0 9334 Ovary T (SC	+2.6-384A Overy T (mc	+22 264A Dyary T	+2.0 386A. Ovary T	+2.0 S115 Ovary T (me	+2,0 265A OvaryT	+2.0 335A Ovary.T	-19 428A Ovary T (m	+1.6 261A Ovary T	+1.6 266A OvaryT	+1.6 \$22 Ovary T.	+14 9485 OT 1-P (SCI	+1.4.262A Ovary I	+1.3 \$25 Overy T	#12. 429A Ovary T (me	+1.2 382A Ovary T	+1.2 288A Ovary T	+1.1 201A Ovary T
Cene	Name	(£CI) 8810017b.	42100138 [153]	42 IQ0188 [LD3]	42100188 (D3)	42100188 (D3)	42100188 [D3]	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (D3)	42100188 (103)	42100188 (D3)	42100188 [153]	42100188 (D3)	42100188 (D3)	42100188 (D3)

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Gene	Bal Probe 1		Probe 2	GEN	Probe1 Probe2	Proba2.	Probe1	:	Probez	23	
Name		P1 P2		A	value	Value	8/8	38	8/3	A&	
421B01817[C31	+18.8 385A Overv T		S91 Fetal tissue	422X0607	26711	1424	103.3	ঠ	2.0	\$	
49.1B0181 (C3)	2		S56 Spinal Cord N	422G0628	13559	1179	63.3	8	6.6	. 89	
42.1B0181 (C3)	+11.1 426A Ovary T (mess)		415A Aorta N	422X0611	14125	1373	67.3	19	5,6	5	
421B0181 (C3)	0.8 205A	0	270A Liver N	42200606	16121	1488	93.3	£	23	5	
421B0181 (C3)	2.		S73 Breast N	422H0623	11326	2235	58.2	8	4.4	89	
421B0181 (C3)			272A Dendriic cells	42240608	6583	1424	24.5	\$	2.1	Ç	
421B0181 (C3)	14.4 Z64A Ovary T	6	S2 Pancress N	422N0629	9865	2245	40.9	Æ	3.6	.	
421B(181. (C3)	44 429A Ovary T (mets)	C	364A Ovary N	42210614	2803	638	22.6	3	7.4	8	
421130181 (C3)	14.2 261A Overy T	75	S10 Skeleral muscle l	42230621	8271	1949	39.5	8	3.6	89	
_	+3.8 -8115 Ovary T (mets)	9	CT10 Small intestine	1422C30604	2281	607	11.6	8	73	3	
42.1B0181 (C3)	+2.5-265A Ovary T	7	CTS Heart N	42200624	3192	1293	19.2	89	0.	8 5	
42 IBD181-{C3}	-2.3 S22 Overv T		CT9 Kidney N	42290627	505	1276	S S	2	3.9	5	
421B0181 (C3)	+2.2 266A Ovary T.	6	S27 Ovary N	42250603	2774	1260	143	5	7.7	9	
	+2.1 9334 Ovary T. (SCID)	(1)	Iz Skdn N	422R0601	1774	837	%	20	21	Š.	
	+1.9 9485 OT 1-P (SCID) *	74	9485 OT 5-P (SCID)	422Y0602	6967	3726	41.5	2	6	2	
421B0181 (C3)	+1.6 382A Ovary T		CT19 Brain'N	42200610	2313	147	6.2	8	2	8	
421B0181 (C3)		3	CT12 Ling N	422V0625	1657	1054	1.6	8	25	S.	
421B0181 (C3)	-1.5 S25 Ovary T	¥.,	CT4 Bone Marrow N 42	422H0619	8	1243	4.5	3	77	Š.	
421B0181 (C3)	+1.4 262A Ovary T	·	334A Large Intestine	H22A0622	3171	2214	16.8	8	00 00	8	
_	+1.2:386A Ovary T	jru	, S40 PBMC (activated	142210605	83	4	4.2	S,	6	<u>ښ</u>	· .
421B0181 (C31	-1.2 335A Oyary T		S7 Overy N	42220626	285	22	3.7	75	20	. 22	
-	-1.0 201A Ovary T	41	S6 Stornach N	422W0620	1197	.1237		3	27	S	
421B0181 (C3)	1.0 428A Overy T (mets)		243A Exophagus N	42240612	2	797	4.5	95	2.4	95	
42) BOJB1 [C3]	383A Overy T. (mets)		II Colon N	422B0609	3430	862	6.8	\$	1.7	র	

Fig. 11

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22	18.0	75	₹	84.	22	47	Ź.	.	1	웊	3	16	₹	69	Ş	8	8.7	28	7.3	62	9	09	99	\$	62
Probe	3/B	3.5	œ.	2.2	34	27.7	4	6.7.	<u>رس</u>	930	5.1	2.7	2.6	च ल	2,2	23	3.5	ei ei	3,2 2,2	2,2	F,	22	ę.	ci œ	3.2
181	AR	75	4	₩	73	ŧ	Ż	9	7	8	E	8	4	3 2°	\$	8	84	28	73	25	8	\$	\$	κ 3 .	8
Probe	S/B	46.3	61.2	62.1	47.3	27.6	57.	20.3	38.8	3.5	34.6	æ. 	12.7	ć,	18.7	2	13.6	7.0	13.2	O,	23	er)	21.6	Ç,	7.4
Probe2	Value	462	SS	1459	88	748	6061	543	22.74	1375	3245	738	11.13	80	1267	1320	1080	8,47	1631	738	1120	261	3529	689	1018
Proba1	Value	7706	10171	14415	1877	4807	9815	266.1	7934	480	8003	1864	2552	380	3516	808	2063	1550	2559	534	893	440	4188	525	1008
GEM	A	422X0611	42200606	422X0607	N 422G0628	422B0609	422H0623	42210614	422N0629	v 422H0619	142230621	in 422C0604	422R0601	42290627	1142240608	42200610	42200624	42250603	IM22A0622	ary 22, 10605	422V0625	42220626	D422Y0602	N42240612	4220V0620
Tobe 2	Name	415A Aorta N	270A LiverN	S91 Petal desuc	S56 Spinal Cord	II Colon N	S73 Bream N	364A Ovary N	S2 Pancreas N	CT4 Bone Marro	S10 Skeletal muscl#223052	CT10 Small intest	2 Skin N	CT9 Kidney N.	272A Dendritic ce	CT19 Brain N	CIS Heart N	S27.Ovary N	334A Large Intest	S40 PBMC (nortive)	TI2 Lung N	ST OWERS IN	A85 OT 5-P (SCI	243A Ecophagus	S6 Stornach N
Ci.	P2 N								96			FIE					7/2				SI FE		ter Olfo		
				THE HINGE	Tark and the last					THE STREET	HINESTRANSPOR	Marcoson nemeral	Leafted by the second					Illicities playeritt				THE PERSON NAMED IN		THE STATE OF THE S	
Probe 1	Name P1	426A Overv T (metr R)	105A Ovary T	385A Ovary T	523 Overy T	83A Ovary T (mote s	263A Ovary T	129A Ovary T (metr &	264A Ovary T	325 Ovary T	6TA Ovary T	3115 Ovary T (mets	334 Ovary T (SCII -	22 Ovary T	84A Overy T (met 85	82A Ovary T	65A Ovary T	66A Ovany T	62A Ovary T	86A Ovary T	88A Ovnry T	35A Ovary T	485-OT 1-P (SCID PS	28A Ovary T (meu	OIA Ovary T
Bal	EXD Na	+16.7	+10.7	6.6+	3.87	+6.4	1.5.1	644	+3.5	2.9	+2.8	5.54	+23	-2.3	+2.2	-22	+1.9	+1.8	+1.5	-1.43	-132	-1.3 3	+1.2 9	+1.1 428A	-1,0
Gerre	Name	42110182-(147)	42110182 1H71	42110182 (H7)	42110182 (H7)	421T0182 (H7)	42110182 (H7)	42110182 [TH7]	42110 (82 (H7)	421T0182 (147)	421T0182 (H7)	42/10182 (H7)	421I0182 (H7)	42110182 (H7)	42110 [82 (147)	42110182 (H7)	42110182 [H7]	42110182-(147)	42,10182 (H7)	42110182 [H7]	42110182 (HT.)	42.110182. [HT.]	42110182 (H7)	42100182 (H7)	42110182 (H7)

13	
Fig.	

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ie2	3	:19	3	3	Ŕ	3	4	Ŋ.	57	L	ę,	\$	<u>2</u>	61.	5	3	4	₹	8	4	2	S	82	<u>.</u>	84	
Probe2	8/B	2.4	2.5	3.5	22	9	20	2.6	70	င်း	e.	23	7.	걺	28	20	2.0	۲. ن	27	20	53	성	긺	8.5	23	•
10	75°	. 19	9	\$	00	8	4	Š	2,	F	ድ	8	2	2	2	5	43	₹.	8	4	E!	8	E	9	48	
Prop	S/B A	55.2	42.6	21.7	7.0	37.8	2.1	52.3	17.4	29.1	38.1	3.4	123	6.7	8.1	17.0	0.8	5.6	11.2	5.9	5.6	5.6	4.2	16.7	23	
Proba2			537	23	1469	923	1210	1737	707	1443	1800	1508	.860	283	723	1342	732	289	202	470	<u>\$</u>	672	丢	31.74	<u>\$</u>	
Probet	Value	8072	7367	2850	11711	88	208	8676	3149	6332	7612	468	2500	1424	1742	3083	1370	307	2097	373	<u>6</u>	750	498	3117	224	•
GEN		422X061.i	I N 422G062B	42210614	422X0607	422H0629	ow 422H0619	42200606	422B0609	scl42230621	422N0629	42200610	422R0601	stin422C0604	42200624	:cl142240608	42250603	var422J0605	stir422A0622	42220626	422V0625	422W0620	N42240612	TD422Y0602	42290627	
Probe 2	P2 · Neme	415A Aorta N	S56 Spinal Con	MAN OWN	S91 Fetal tissue	S73 Breast N	CT4 Boue Minn	270A Liver N	II Colon N	S10 Skeletal mu	S2 Pancres N	CT19 Brain N	I2 Skin N	CT10 Small inte	CTS Heart N	272A Demilritie	S27 Ovary N	S40 PBMC (act	334A Large Inte	ST Ovary.N	CT12 Lung N	Se Stornach N	243A Esophagu	9485 OT 5-P (SC	CT9 Kidney N	
	P.2	Transport of the last of the l				Commenter (1891)		THE PERSON NAMED IN COLUMN	Auritus al lustant și			Continue de la Contin			Challenger of professional	fathers disting	Marie Strategic Col	PSTEPRINESSON INTO	Control of the Party of the Par		Continue of the second	A STATE STATE OF	ACTUAL STREET,	THE PROPERTY OF THE PARTY OF TH	(Kerta Nie Patronell	
Bal Probe 1	Exp Name P1	+33.2, 426A Overy T (mets	+13.7- \$23.0vary T	+12.6.429X Ovary T (mets	+8.0, 385.A. Overy T		-5.8.525 Ovary T	+5:0.205A Ovary T	+4.5 383A Overy T (mets 12	44.4 261A Ovary T	+4.2 264A Overy T	-3.2. 382A Overy T	+2:9 9334 Overy T (SCIL 68)	+2.5 Si15 Ovary T (mets.	+2.4 265A Ovury T	+2.3 384A. Ovary T (metr	+1.9 266A Ovary T	-1.9 386A Ovary T	+1.7 262A Ovary 7	-L3 335A, Ovary T	-1.1 288A Ovary T.	+1.1 201A Ovary T	+1.1 4384 Ovary I (mets	-1.0 9485 OT 1-P (SCID 12)	\$22. Overy T	
Genre	Name	421V0189 (DE)	421V0189 (DI)	421 X0189 (DU)	421V0189 (1)1)	421V0189 (D1)	421V0189 (D1.)	421VQ189 (D1)	421V01R9 (D1)	421V0[89-{D1]	421V0189.[D1]	421 V0189 (DJ)	421V0189 (D1)	421V0189 (DJ)	421V0189 (D1)	421V0189 (D)	421V0189 (D1)	421V0189 [D]]		421V0189 (D1)	421V01897[D1]	421 V0189 (DJ)	421V0189 (DJ)	421V0189 (D1)	421V0189 (D1)	

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62	A&	જ	Š	8	.	50	\$	≈	25	B	4	S	\$	SI	42	4	ጽ	G	78	5	58	5	, 33,	36	4 .
Prof	8/8	23	2.3	2.5	7	2.0	2.0	20	Ç.	9	7.1	3 . 0	6.1	2.5	20	2.2	2.6	2.6	<u>ရ</u>	20	2,3	6,3	1.7	27	2.2
bei	23	જ	%	80	.	:S	84	\$	Κ,	8	74	\$	\$	S	47	4	ĸ	53	8	8	88	7	88	<u>ښ</u>	4
2	8/8	36.3	27.1	10.1	33.	31.1	11.9	2.6	17.7	23.0	<u>ဆ</u>	14.9	13.4	4	37	52	10:L	1,4	2,7	2,9	4.2	13.1	125	7:6	23
Probe2	Value		533	130	1668	1235	438	1259	1036	1239	627	000	1270	605	683	86	1245	805	325	501	677	2493	562	36.	845
Probel	Value	\$441	83.8	1252	9507	\$456	- XX	8	3733	4163	1565	3455	2667	291	410	1622	1892	\$	236	382	558	2582	1977	1739	283
GEN	A	422X061.1	N 422GD628	42210614	422X0607	42200606	42200624	42200610	cl42230621	422H0623	tin422C0604	422N0529	1142240608	42290627	A22210605	422RD601	tir422A0622	422 V0625	N42240612	42220626	422W0620	D422Y0602	422B0609	42250603	w 422H0619
Probe 2	Name	15A Aorra N	56. Spinal Cord	64A Owery N	91 Fetal ussue	270A.Liver N	T5 Heart N	T19 Brain N	10 Skeletal mus	73 Breast N	T10 Small intes	2 Punctons N	272A Dendritic o	TO Ridney N.	巫	2 Sidn Z	34A Large Intes	TI2 Lung N	43A Esophagus	7 Overy N	Sibrateb N	185 O'T 5-P (SC	Colon N	27 Ovary N	I'4 Bone Marro
Al	P2. No	图 4			×	70				20	O I		(·)	٠ •	20	12	m		2	S	i de	ò		23	to the same of the
		Talitament street	THE STREET STREET	California de Cari				Kalen in the last	THE PARTY OF THE P		CONTRACTOR OF STREET	The state of the state of	rnaska indelig ili e		HETT THE STORY				Harring Street		(Name and Assessed				
obe 1	me P1	6A Ovary T (metr 2	3.Ovary T	9A Overy T (mets	SA Ovary T	SA Overy T	SA Ovary T	2A Overy T	1A Ovary T	3A Oracy T	15 Ovary T (mets or	4A Ovany T	4A. Ovary T (mos. 2)	2 Ovary T	SA Ovatry 1	24 Overy T (SCIT of	2A Ovary T	8A Overry T	8A Ovary T (mets	SA Ovary T.	A Ovary T	SOT 1-P (SCID P	IA Ovary T (men	SA: Ovary T	5 Owary T
Bel Pr	Exp Na	+20.2 42	ES 0.01+	+8.3 42	+5.7 38	+4.4.205	+4.2.26	41.38	+3.6.26	+34.26	+25 51	+2.1.26	+2.1.38	12.J. S.2.	-1.7 38	+1.6 93	+1.5 26	-15 28	-1.4 42	-1.3 33	-1.2 20	¥ 0.1+	38:	566	22
Gene	Name	421H0187 [E11]	421H0187 (B11)	421H0187 [III1]	421H0187 [E11]	421H0187 (E11)	42(HO187 (E11)	42JE0187 (E11)	421H0187 (E11)	421H0187 (E11)	421H0187 (E11.)	421H0187 (ELT)	42 LHO187 [E] 1.1	421H0187 (ELL)	42 LH0187 (E11)	421H0187 (E11)	42(H0(87 (E(1))	42 (E) (E) 1)	42JH0187 (E11)	4211(0187 (E11)	421H0187 [L11]	421H0187 [E11]	42(H0) 87 (E11)	42H0187 (E(1)	421H0187 [E]1]

F1g. 14

35/101

11721-1

11721-2

AAGGCTGGTGGTTTTTTGATCCTGCTGGAGAACCTCCGCTTTCATGTGGAGGAAGAAGGGAAAGATGC
TTCTGGGAACAAGGTTAAAGCCGAGCCAGCCAAAATAGAAGCTTTCCGAGCTTCACTTTCCAAGCTAGGGGATG
TCTATGTCAATGATGCTTTTTGGCACTGCTCACAGAGCCCCACAGCTCCATGGTAGGAGTCAATCTGCCACAGAAG
GCTGGTGGGTTTTTGATGAAGAAGGAGCTGAACTACTTTGCAAAGGCCTTGGAGAGCCCAGAGCGACCCTTCCT
GGCCATCCTGGGCGAGCTAAAGTTGCAGACAAGATCCAGCTCATCAATAATATGCTGGACAAAGTCAATGAGA
TGATTATTGGTGGTGGAATGGCTTTTACCTTCCTTAAGGTGCTCAACAACATGGAGATTGGCACTTCTCTGTTT
GATGAAGAGGGAGCCAAGATTGTCAAAGACCTAATGTCCAAAGCTGAGAAGAATGGTGTGAAGATTACCTTGCC
TGTTGACTTTGTCACTGCTGACAAGTTTGATGA

11724-1

11724-2

Fig. 15A

36/101 11725-32-1.2

11726 - 182

11727-182

AAGTGTTAGCATTAATGTTTTATTGTCACGCAGATGGCAACTGGGTTTATGTCTCATATTTTATATTTTTGTA
AATTAAAAAAATTMCAAGTTTTAAATAGCCAATGGCTGGTTATATTTTCAGAAAACATGATTAGACTAATTCAT
TAATGGTGGCTTCAAGCTTTTCCTTATTGGCTCCAGAAAAATTCACCCCACCTTTTGTCCCTTCTTAAAAAAACTGG
AATGTTGGCATGCATTTGACTTCACACTCTGAAGCAACATCCTGACAGTCATCCACACTCTACTTCAAGGAATAT
CACGTTGGAATACTTTTCAGAGAGGGAATGAAAGAAAGACTTGATCATTTTTGCAAGGCCCACACCACGTGGCTG
AGAAGTCAACTACTACAAGTTTATCACCTGCAGCGTCCAAGGCTTCCTGAAAAGCAGTCTTGCTCTCGATCTGC
TTCACCATCTTGGCTGCTGGAGTCTGACGAGCGGCTGTAAGGACCGATGGAAATGGATCCAAAAGCACCAAACAG
AGCTTCAAGACTCGCTGCTTGGCATGAATTCGGATCCGA

Fig. 15B

37/101 11728.1.40.19.19

11728.2.40.19.19

CCCGTGGGTGCCATCCACGGAGTTGTTACCTGATCTTTGGAAGCAGGATCGCCCGTCTGCACTGCAGTGGAAGC
CCCGTGGGCAGCAGTGATGGCCATCCCCGCATGCCACGGCCTCTGGGAAGGGGCAGCAACTGGAAGTCCCTGAG
ACGGTAAAGATGCAGGAGTGGCCGGCAGAGCAGTGGGCATCAACCTGGCAGGGGCCACCCAGATGCCTGCTCAG
TGTTGTGGGCCATTTGTCCAGAAGGGGACGGCAGCAGCTGTAGCTGGCTCCTCCGGGGTCCAGGCAGCAGCAG
CAGGGCAGAACTGACCATCTGGGCACCGCGTTCCAGCCACCAGCCCTGCTGTTAAGGCCACCCAGCTCACCAGG
GTCCACATGGTCTGCCTGCGTCCGACTCCGCGGTCCTTGGGCCCTGATGGTTCTACCTGCTGTGAGCTGCCCAG
TGGGAAGTATGGCTGCCAATGCCCAACGCCACCTGCTGCTCCGATCACCTGCTGCCCCAAGACACT
GTGTGTGACCTGATCCAGAGTAAGTGCCTCTCCAAGGAGAACG

11730-1

11730-2

Fig. 15C

38/101

11732.1contig

11732.2contig

11735-1-2

11740.2.contig

Fig. 15D

39/101 11765.2&64.2.contig

CGCCTCCACCATGTCCATCAGGGTGACCCAGAAGTCCTACAAGGTGTCCACCTCTGGCCCCCGGGCCTTCAGCA
GCCGCTCCTACACGAGTGGGCCCGGTTCCCGCATCAGCTCCTCGAGCTTCTCCCGAGTGGGCAGCAACTTT
CGCGGTGGCCTGGGCGGCGGCGTATGGTGGGGGCCAGCGCATCACCGGAGTTACGGTCAACCAGAG
CCTGCTGAGCCCCCTTGTCCTGGAGGTGGACCCCAACATCCAGGCCGTGCGCACCCAGGAGAAGAAGGAGCAGATCA
AGACCCTCAACAACAAGTTTGCCTCCTTCATAGACAAGGTACGGTTCCTGGAGCAGCAGCAGAACAAGATGCTGGAG
ACCAAGTGGAGCCTCCTGCAGCAGCAGAAGACGGCTCGAAGCAACATGGACAACATGTTCGAGAGCATCAA
CARCCTTAGGCGGCAGCTGGAGACTCTGGGCCAGGAGAACAACATGTTCGAGAGCTTGGCAACATCAA
CARCCTTAGGCGGCAGCTGGAGACTCTGGGCCAGGAGAACATGAGCTGAAGCTGGAGGCGGAGCTTGGCAACATGCAGG
GGCTGGTGGAGGACTTCAAGAACAAGTATGAGGATGAGATCAATAAGCGTACAGAGATCTCGCCTGGAAGGCTGACCGA
CGAGATCAACTTCCTCAGGCAGCTGTATGAAGAGAGAGATCCGGGAGCTCCCAGATCTCGGACACATCTG
TGGTGCTGTCCATGGACAACAGCCGCTCCCTGGACATGACCAGCTCCAAGTCCCAGATCTCGGACACATCTG
TGGTGCTGTCCATGACAACACGCCGCTCCCTGGACACATGACCAGTCAAGTATGAGGAGCTCCAGAGCCTGCAGACCTGGC
TGGGAAGCACGGGGATGACCTGCAGAGCATGAACCAGGTCAAGTATGAGGAGCTGCAGACCTGGC
TGGGAAGCACGGGGATGACCTGCGGCCCACAAAGACTTACCTGAGATCAACCCGGAACATCAGCCCGGCT
XCAGGCTGAGATTGAGGGCCTCAAAGGCCAGAXGCTTXCCTGGAXGXCCCGCCAT

11767.2.contig

CCCGGAGCCACCAACGAGCGAAAATGGCAGACAATTTTTCGCTCCATGATGCGTTATCTGGGTCTGGAAACC
CAAACCCTCAAGGATGGCCTGGCGCATGGGGGAACCAGCCTGCTGGGGCAGGGGGCTACCCAGGGGCTTCCTAT
CCTGGGGCCTACCCCGGGCAGCACCCCCAGGGGCTTATCCTGGACAGGCACCTCCAGGCGCCCTACCCTGGAGC
ACCTGGAGCTTATCCCGGAGCACCTGCACCTGGAGTCTACCCAGGGCCACCCAGCGGCCCCTGGGGCCTACCCAT
CTTCTGGACAGCCAAGTGCCACCGGAGCCTACCCTGCCACTGGCCCCCTATGGCGCCCCTGCTGGGCCACTGATT
GTGCCTTATAACCTGCCTTTGCCTGGGGGAGTGGTGCCTCGCATGCTGATAACAATTCTGGGCACGGTGAAGCC
CAATGCAAACAGAATTGCTTTAGATTTCCAAAGAGGGAATGATGTTGCCTTCCACTTTAACCCACGCTTCAATG
AGAACAACAGGAGAGTCATTGGTTGCAATACAAAGCTGGATAA

11768 - 1&2

40/101 11768-1&2-11735-1&2

11769.1.contig

11769.2.contia

AGCGCGGTCTTCCGGCGCGAGAAAGCTGAAGGTGATGTGGCCGCCCTCAACCGACGCATCCAGCTCGTTGAGGA
GGAGTTGGACAGGGCTCAGGAACGACTGGCCACGGCCCTGCAGAAGCTGGAGGAGGCAGAAAAAGCTGCAGATG
AGAGTGAGAGAGAATGAAGGTGATAGAAAACCGGGCCATGAAGGATGAGGAGAAGATGGAGAATTCAGGAGATG
CAGCTCAAAGAGGCCAAGCACATTGCGGAAGAGGCTGACCGCAAATACGAGGAGGTAGCTCGTAAGCTGGTCAT
CCTGGAGGGTGAGCTGGAGAGAGGCGTGCGGAGGTGTCTGAACTAAAATGTGGTGACCTGGAAGAAG
AACTCAAGAATGTTACTAACAATCTGAAATCTCTGGAGGCTGCATCTGAAAAGTATTCTGAAAAGGAGGACAAA
TATGAAGAAGAAATTAAACTTCTGTCTGACAAACTGAAAGAGGCTGAGACCCGTGCTGAATTTGCAGAGAGAAAC
GGTTGCAAAACTGGAAAAGACAATTGATGACCTGGAAGAGAAACTTGCCCAGC

11770.1.contig

Fig. 15F

41/101 11770.2.contig

GCAAGGAACTGGTCTCACACTTGCTGGCTTGCGCATCAGGACTGGCTTTATCTCCTGACTCACGGTGCAAA GGTGCACTCTGCGAACGTTCACGTCCCCAGCGCTTGGAATCCTACGGCCCCCACAGCCGGATCCCCTCAGC CTTCCAGGTCCTCAACTCCCGTGGACGCTGAACAATGGCCTCCATGGGGCTACAGGTAATGGGCATCGCGCTGG CCGTCCTGGGCTGGCCGTCATGCTGCTGCTGCCGCTGCCCATGTGGCGCGTGACGGCCTTCATCGGCAGC AACATTGTCACCTCGCAGACCATCTGGAGGGCCTATGGATGAACTGCGTGGTGCAGAGCACCGGCCAGATGCA GTGCAAGGTGTACGACTCGCTGCTGCACGCACACTCATCA

11773.1.contig

11778.1.contig

11778-2&30-2

Fig. 15G

42/101

11782.1.contig

ATCTACGTCATCAATCAGGCTGGAGACACCATGTTCAATCGAGCTAAGCTGCTCAATATTGGCTTTCAAGAGGC
CTTGAAGGACTATGATTACAACTGCTTTGTGTTCAGTGATGTGGACCTCATTCCGATGGACGACCGTAATGCCT
ACAGGTGTTTTTCGCAGCCACGGCACATTTCTGTTGCAATGGACAAGTTCGGGTTTAGCCTGCCATATGTTCAG
TATTTTGGAGGTGTCTCTGCTCTCAGTAAACAACAGTTTCTTGCCATCAATGGATTCCCTAATAATTATTGGGG
TTGGGGAGGAGAAGATGACGACATTTTTAACAGATTAGTTCATAAAGGCATGTCTATATCACGTCCAAATGCTG
TAGTAGGGAGGTGTCGAATGATCCGGCATTCAAGAGACAAGAAAAATGAGCCCAATCCTCAGAGGTTTGACCGG
ATCGCACATACAAAGGAAACGATGCGCTTCGATGGTTTGAACTCACTTACCTACAAGGTGTTGGATGTCAGAGA
TACCCGTTATATACCCAAATCAC

11782.2.contig

11783-1 & 2

11786.1.contig

GCTCTTCACACTTTTATTGTTAATTCTCTTCACATGGCAGATACAGAGCTGTCGTCTTGAAGACCACCACTGAC CAGGAAATGCCACTTTTACAAAATCATCCCCCCTTTTCATGATTGGAACAGTTTTCCTGACCGTCTGGGAGCGT TGAAGGGTGACCAGCACATTTGCACATGCAAAAAAAGGAGTGACCCCAAGGCCTCAACCACACTTCCCAGAGCTC ACCATGGGCTGCAGGTGACCTTGCCAGGTTTGGGGTTCGTGAGCTTTCCTTGCTGCTGCGGTGGGGAGGCCCTCA AGAACTGAGAGGCCGGGTATGCTTCATGAGTGTTAACATTTACGGGACAAAAAGCGCATCATTAGGATAAGGAA CAGCCACAGCACTTCATGCTTGTGAGGGTTAGCTGTAGGAGCGGGTGAAAGGATTCCAGTTTATGAAAATTTAA AGCAAACAACGGTTTTTAGCTGGGTGGGAAACAGGAAAACTGTGATGTCGGCCAATGACCACCATTTTTCTGCC CATGTGAAGGTCCCCATGAAACC

Fig. 15H

43/101

11786.2.contig

13691.182

13692.182

13693.2

Fig. 15I

44/101 13696.1-13744.1

13700.1

CAAGGGATATATGTTGAGGGTACRGRGTGACACTGAACAGATCACAAAGCACGAGAAACATTAGTTCTCTCCCT
CCCCAGCGTCTCCTTCGTCTCCCTGGTTTTCCGATGTCCACAGAGTGAGATTGTCCCTAAGTAACTGCATGATC
AGAGTGCTGKCTTTATAAGACTCTTCATTCAGCGTATCCAATTCAGCAATTGCTTCATCAAATGCCGTTTTTTGC
CAGGCTACAGGCCTTTTCAGGAGAGATTTAGAATCTCATAGTAAAAGACTGAGAAATTTAGTGCCAGACCAAGAC
GAATTGGGTGTGTAGGCTGCATTNCTTTCTTACTAATTTCAAATGCTTCCTGGTAAGCCTGCTGGGAGTTCGAC
ACAAGTGGTTTTGTTTGTTGCTCCAGATGCCACTTCAGAAAGATACCTAAAATAATCTCCTTTCATTTTCAAAGT
AGAACAC

13700.2

TCCGGAGCCGGGGTAGTCGCCGCCGCCGCCGCCGCCGGTGCAGCCACTGCAGGCACCGCTGCCGCCGCCTGAGTAGT
GGGCTTAGGAAGAAGAAGAGGTCATCTCGCTCGGAGCTTCGCTCGGAAGGGTCTTTGTTCCCTGCAGCCCTCCCAC
GGGAATGACAATGGATAAAAGTGAGCTGGTACAGAAAGCCAAACTCGCTGAGCAGGCTGAGCGATATGATGATA
TGGCTGCAGCCATGAAGGCAGTCACAGAACAGGGGCATGAACTCTCCAACGAAGAGAAAATCTGCTCTCTGTT
GCCTACAAGAATGTGGTAAGGCCGCCCGCCGCTCTTCCTGCGTGTCATCTCCAGCATTGAGCAGAAAACAGAG
AGGAATGAGAAGAAGCAGCAGAAGAGCAAAAGAGTACCGTGAGAAGATAGAGGCAGAACTGCAGGACATCTGCAA
TGATGTTCTGGAGCTTGTTGGACAAATATCTTATTCCAATGCTACACAACCCAGAAA

13701.1

45/101

13701.2

13702.2

AGCTGGCGCTAGGGCTCGGTTGTGAAATACAGCGTRGTCAGCCCTTGCGCTCAGTGTAGAAACCCACGCCTGTA AGGTCGGTCTTCGTCCATCTGCTTTTTTCTGAAATACACTAAGAGCAGCCACAAAACTGTAACCTCAAGGAAAC CATAAAGCTTGGAGTGCCTTAATTTTTAACCAGTTTCCAATAAAACGGTTTACTACCT

13704.2-13740.2

GGAGATGAAGATGAGGAAGCTGAGTCAGCTACGGGCARGCGGGCAGCTGAAGATGATGAGGATGACGATGTCGA TACCAAGAAGCAGAAGACCGACGACGATGACTAGACAGCAAAAAAGGAAAAGTTAAA

13706.1

GATGAAAATTAAATACTTAAATTAATCAAAAGGCACTACGATACCACCTAAAAACCTACTGCCTCAGTGGCAGTA KGCTAAKGAAGATCAAGCTACAGSACATYATCTAATATGAATGTTAGCAATTACATAKCARGAAGCATGTTTGC TTTCCAGAAGACTATGGNACAATGGTCATTWGGGCCCAAGAGGATATTTGGCCNGGAAAGGATCAAGATA AANGTAAAG

13706.2

Fig. 15K

46/101

13707.3

13710.2

13710-1

TGAGATTTATTGCATTTCATGCAGCTTGAAGTCCATGCAAAGGRGACTAGCACAGTTTTTAATGCATTTAAAAA ATAAAAGGGAGGAGGAGCAAACACACAAAGTCCTAGTTTCCTGGGTCCCTGGGAGAAAAGAGTGTGGCAATG AATCCACCCACTCTCCACAGGGAATAAATCTGTCTCTTTAAATGCAAAGAATGTTTCCATGGCCTCTGGATGCAA ATACACAGAGCTCTGGGGTCAGAGCAAGGGATGGGGAGAGACAACAGCTCTCAC CTAATTCCATCTGAGGGCAAGAACAACGTGGCAAGTCTTGGGGGTAGCAGCTGTT

13711.1

Fig. 15L

47/101

13711.2

TGAGACGACCACTGGCCTGGTCCCCCCTCATKTGCTGTCGTAGGACCTGACATGAAACGCAGATCTAGTGGCA
GAGAGGAAGATGATGAGGAACTTCTGAGACGTCGGCAGCTTCAAGAAGAGCAATTAATGAAGCTTAACTCAGGC
CTGGGACAGTTGATCTTGAAAGAAGAGAGATGGAGAAAGAGGCCGGGAAAGGTCATCTCTCGTTAGCCAGTCGCTA
CGATTCTCCCATCAACTCAGCTTCACATATTCCATCATCTAAAACTGCATCTCTCCCTGGCTATGGAAGAAATG
GGCTTCACCGGCCTGTTTCTACCGACTTCGCTCAGTATAACAGCTATGGGGATGTCAGCGGGGGAGTGCGAGAT
TACCAGACACTTCCAGATGGCCACATGCCTGCAATGAGAATGGACCGAGGAGTGTCTATGCCCAACATGTTGGA
ACCAAAGATATTTCCATATGAAATGCTCATGGTGACCAACAGAGGGCCGAAACCAAATCTCAGAGAGGTGGACA
GAA

13713.182

TCACTTTATTTTCTTGTATAAAAACCCTATGTTGTAGCCACAGCTGGAGCCTGAGTCCGCTGCACGGAGACTC
TGGTGTGGGTCTTGACGAGGTCAGTGAACTCCTGATAGGGAGACTTTGGTGAATACAGTCTCCTTCCAGAGG
TCGGGGGTCAGGTAGCTGTAGGTCTTAGAAATGGCATCAAAGGTGGCCTTGGCGAAGTTGCCCAGGGTGGCAGT
GCAGCCCCGGGCTGAGGTGTAGCAGTCATCGATACCAGCCATCATGAG

13715.4

13717.182

TGAATGGGGAGGACCTGACCCAGGAAATGGAGCTTGNGGAGACCAGGCCTGCAGGGGATGGAACCTTCCAGAAG
TGGGCATCTGTGGTGGTGCCTCTTGGGAAGGAGCAGAAGTACACATGCCATGTGGAACATGAGGGGCTGCCTGA
GCCCCTCACCCTGAGATGGGGCCAAGGAGGAGCCCTCCTTCATCCACCAAGACTAACACAGGTAATCATTGCTGTTC
CGGTTGTCCTTGGAGCTGTGGTCATCCTTGGAGCTGTGATGGCTTTTTGTGATGAAGAGGAGGAGAAACACAGGT
GGAAAAGGAGGGGACTATGCTCTGGCTCCAGGCTCCCAGAGCTCTGATATGTCTCTCCCAGATTGTAAAGTGTG
AAGACAGCTGCCTGGTGTGGACTTGGTGACAGACAATGTCTTCACACATCTCCTGTGACATCCAGAGACCTCAG
TTCTCTTTAGTCAAGTGTCTGATGTTCCCTGTGAGTCTGCGGGCTCAAAGTGAAGAACTGTGGAGCCCAGTCCA
CCCCTGCACACCAGGACCCTATCCCTGCACTGCCCTGTGTTCCCTTCCACAGCCAACCTTGCTGCTCCAGCCAA
ACATTGGTGGACATCTGCAGCCTGTCAGCTCCATGCTACCCTGACCTTCCACACTCCACTTCCACACTGAGAAT
AATAATTTGAATGTGGGTGGCTCACAACCATCTGTAATGGGATCTAATACCCTCTTCCACAGTGTCTGAAGACASCT
ACAGTGTACTTACATATAATAATAATAAATAAA

Fig. 15M

48/101 13719.182

13721.1

13721.2

13723.1

CATGGGTTTCACCAGGTTGGCCAGGCTGCTCTTGAACTSCTGACCTCAGGTGATCCACCCGCCTCGGCCTCCCA
AAGTGCTGGGATTACAGGCGTGAGCCACCACGCCCGGCCCCCAAAGCTGTTTCTTTTTGTCTTTAGCGTAAAGCT
CTCCTGCCATGCAGTATCTACATAACTGACGTGACTGCCAGCAAGCTCAGTCACTCCGTGGTCTTTTTCTCTTT
CCAGTTCTTCTCTCTCTCTCTAGAGTTCTGCCTCAGTGAAAGCTGCAGGTCCCCAGTTAAGTGATCAGGTGAGGG
TTCTTTGAACCTGGTTCTATCAGTCGAATTAATCCTTCATGATGG

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13723.2

13725.1

13725.2

13726.1&2

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13727.1

13727.2

ACCTAGACAGAAGGTGGGTGAGGGAGGACTGGTAGGAGGCTGAGGCAATTCCTTGGTAGTTTGTCCTGAAACCC
TACTGGAGAAGTCAGCATGAGGCACCTACTGAGAGAAGTGCCCAGAAACTGCTGACTGCATCTGTTAAGAGTTA
ACAGTAAAGAGGTAGAAGTGTTTTCTGAATCAGAGTGGAAGCGTCTCAAGGGTCCCACAGTGGAGGTCCCTGA
GCTACCTCCCTTCCGTGAGTGGGAAGAGTGAAGCCCATGAAGAACTGAGATGAAGCAAGGATGGGGTTCCTGGG
CTCCAGGCAAGGGCTGTGCTCTCTGCAGCAGGAGGCCCCACGAGTCAGAAGAAAAAGAACTAATCATTTGTTGCA
AGAAACCTTGCCCGGATACTAGCGGAAAACTGGAGGCGGNGGTGGGGGCACAGGAAAGTGGAAGTGATTTGATG
GAGAGCAGAGAAGCCTATGCACAGTGGCCGAGTCCACTTGTAAAGTG

13728.182

13731.182

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13734.182

13736.2

13744.2-13696.2

13746.1&2-13720.1&2

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14347.1

CAGATTTTTATTTGCAGTCGTCACTGGGGCCGTTTCTTGCTGCTTATTTGTCTGCTAGCCTGCTCTTCCAGCTG
CATGGCCAGGCGCAAGGCCTTGATGACATCTCGCAGGGCTGAGAAATGCTTGGCTTGCTGGGCCAGAGCAGATT
CCGCTTTGTTCACAAAGGTCTCCAGGTCATAGTCTGGCTGCTCGGTCATCTCAGAGAGCCTCAAGCCAGTCTGGT
CCTTGCTGTATGATCTCCTTGAGCTCTTCCATAGCCTTCTCCTCCAGCTCCCTGATCTGAGTCATGGCTTCGTT
AAAGCTGGACATCTGGGAAGACAGTTCCTCCTCTTCCTTGGATAAATTGCCTGGAATCAGCGCCCCGTTAGAGC
AGGCTTCCATCTCTTCTGTTTCCATTTGAATCAACTGCTCTCCACTGGGCCCCACTGTGGGGGCTCAGCTCCTTG
ACCCTGCTGCATATCTTAAGGGTGTTTAAAGGATATTCACAGGAGCTTATGCCTGGT

14347.2

14348.2&14350.1&2

14349.1&2

TTCGTGAAGACCCTGACTGGTAAGACCATCACTCTCGAAGTGGAGCCCGAGTGACACCATTGAGAATGTCAAGG
CAAAGATCCAAGACAAGGAAGGCATCCCTCCTGACCAGCAKAGGTTGATCTTTGCTGGGAAACAGCTGGAAGAT
GGACGCACCCTGTCTGACTACAACATCCAGAAAGAGTCCACCCTGCACCTGGTGCTCCGTCTCAGAGGTGGGAT
GCAAATCTTCGTGAAGACCCTGACTGGTAAGACCATCACCCTCGAGGTGGAGCCCAGTGACACCATCGAGAATG
TCAAGGCAAAGATCCAAGATAAGGAAGGCATCCCTCCTGATCAGCAGAGGTTGATCTTTGCTGGGAAACAGCTG
GAAGATGGACCCCTGTCTGACTACAACATCCAGAAAGAGTCCACTTTGCACTTGCACTTGCGCTTTGAGGGG
GGGTGTCTAAGTTTCCCCTTTTAAGGTTTCAACAAATTTCATTGCACTTTCCTTTCAATAAAGTTGTTGCATTC

Fig. 15R

53/101 14352.1&2

14353.1

14353.2

17182.182

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17183.2

GGTTCACAGCACTGCTGCTTGTGTTGCCGGCCAGGAATTCCAGGCTCACAAGGCTATCTTAGCAGCTCGTTC
TCCGGTTTTTAGTGCCATGTTTGAACATGAAATGGAGGAGGAGAGAAAAAGAATCGAGTTGAAATCAATGATGTGG
AGCCTGAAGTTTTTAAGGAAATGATGTGCTTCATTTACACGGGGAAGGCTCCAAACCTCGACAAAATGGCTGAT
GATTTGCTGGCAGCTGCTGACAAGTATGCCCTGGAGCGCTTAAAGGTCATGTGTGAGGATGCCCTCTGCAGTAA
CCTGTCCGTGGAGAAACGCTGCAGAAATTCTCATCCTGGCCGACCTCCACAGTGCAGATCAGTTGAAAACTCAGG
CAGTGGATTTCATCAACTATCATGCTTCGGATGTCTTGGAGACCTCTTGGG

17186.1&2

17187.1&2

17191.1889.1

55/101 17192.1&2

17193

56/101

16443.1.edit

16443.2.edit

16444.2.edit

AGCGTGGTTNCGGCCGAGGTCCCAACCAAGGCTGCANCCTGGATGCCATCAAAGTCTTCTGCAACATGGAGACT GGTGAGACCTGCGTGTACCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAGGA CAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGACC CTGCCGATGTGGACCTGCCCGGGCGGNCGCTCGA

16445.1.edit

AGCGTGGTCGCGGCCGAGGTCAAGAACCCCGCCCGCACCTGCCGTGACCTCAAGATGTGCCACTCTGACTGGAA GAGTGGAGAGTACTGGATTGACCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAGA CTGGTGAGACCTGCGTGTACCCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAG GACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGA CCCTGCCGATGTGGACCTGCCCGGGCGGCCGCTCGA

Fig. 15V

57/101

16445.2.edit

16446.1.edit

TCGAGCGCCCCCGGCAGGTCCTCCTCAGAGCGGTAGCTGTTCTTATTGCCCCGGCAGCCTCCATAGATNAA GTTATTGCANGAGTTCCTCCACGGTCAAAGTACCAGCGTGGGAAGGATGCACGGCAAGGCCCAGTGACTGCGT TGGCGGTGCAGTATTCTTCATAGTTGAACATATCGCTGGAGTGGACTTCAGAATCCTGCCTTCTGGGAGCACTT GGGACAGAGGAATCCGCTGCATTCCTGCTGGTGGACCTCGGCCGCGACCACGCT

16446.2.edit

AGCGTGGTCGCGGCCGAGGTCCACCAGCAGGAATGCAGCGGATTCCTCTGTCCCAAGTGCTCCCAGAAGGCAGG ATTCTGAAGACCACTCCAGCGATATGTTCAACTATGAAGAATACTGCACCGCCAACGCAGTCACTGGGCCTTGC CGTGCATCCTTCCCACGCTGGTACTTTGACGTGGAGAGGAACTCCTGCAATAACTTCATCTATGGAGGCTGCCG GGGCAATAAGAACAGCTACCGCTCTGAGGAGGACCTGCCCGGGCGGCCGCTCGA

16447.1.edit

Fig. 15W

58/101

16447.2.edit

16449.1.edit

16450.1.edit

16450.2.edit

Fig. 15X

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16451.1.edit

16451.2.edit

TCGAGCGCCCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT TGTCATGGCACCACTCTGAAATCACACCATTGTCATGCACCACTCTCCAAAGCCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACATTCCCCACTCATCTCCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTCAAGCCTTCGNTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGTACCTCTGGTGAGGACCTCGGCCGCACCACG CT

16452.1.edit

16452.2.edit

Fig. 15Y

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16453.1.edit

16453.2.edit

16454.1.edit

AGCGTGGNTGCGGACGCCCACAAAGCCATTGTATGTAGTTTTANTTCAGCTGCAAANAATACCNCCAGCATCCACCTTACTAACCAGCATATGCAGACA

16454.2.edit

TCGAGCGGTCGCCCGGGCAGGTCTGGGCGGATAGCACCGGGCATATTTTGGAATGGATGAGGTCTGGCACCCTG
AGCAGCCCAGCGAGGACTTGGTCTTAGTTGAGCAATTTGGCTAGGAGGATAGTATGCAGCACGGTTCTGAGTCT
GTGGGATAGCTGCCATGAAGNAACCTGAAGGAGGCGCTGGCTGGTANGGGTTGATTACAGGGCTGGGAACAGCT
CGTACACTTGCCATTCTCTGCATATACTGGNTAGTGAGGCGAGCCTGGCGCTCTTCTTTGCGCTGAGCTAAAGC
TACATACAATGGCTTTGNGGACCTCGGCCGCGACCACGCTT

Fig. 15Z

61/101 16455.1.edit

TCGAGCGCCCCCGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT TGTCATGACACCACTCTGACACTCTGACACTCTCCAAAGCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACACTTCCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGC CTCTGCTGGTCTTCAAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCCACCA CGCT

16455.2.edit

16456.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGCTTNCTGCTCANGTGATTATCCTGAACCATCCAGGCCAAATAAGCGCCGGCCTATGCCCCTGNATTGGATTGCCACACGGCTCACATTGCATGCAAGTTTGCTGAGCTGAAGGAAAAGATTGATC

16456.2.edit

Fig. 15AA

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16459.1.edit

16459.2.edit

16460.1.edit

TCGAGCGCCCCCGGGCAGGTCCATTTTCTCCCTGACGGNCCCACTTCTCTCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCNTCCCCGAACCTTATGC
CTCTGCTGGGCTTTCAGNGCCTCCACTATGATGNTGTAGGGGGGCACCTCTGGNGANGACCTCGGCCGCACCA
CGCT

16460.2.edit

Fig. 15BB

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16461.1.edit

16461.2.edit

16463.1.edit

AGCGTGGNNGCGGCCGAGGTATAAATATCCAGNCCATATCCTCCCTCCACACGCTGANAGATGAAGCTGTNCAA AGATCTCAGGGTGGANAAAACCAT

16463.2.edit

Fig. 15CC

64/101

16464.1.edit

CGAGCGGGCGACCGGGCAGGTNCAGACTCCAATCCANANAACCATCAAGCCAGATGTCAGAAGCTACACCATCA CAGGTTTACAACCAGGCACTGACTACAAGANCTACCTGCACCACCCTTGAATGACAATGCTCGGAGCTCCCCTGTG GTCATCGACGCCTCCACTGCCATTGATGCACCATCCAACCTGCGTTTCCTGGCCACCACCCCAATTCCTTGCT GGTATCATGGCAGCCGCCACGTGCCAGGATTACCGGTACATCATCNAGTATGANAAGCCTGGGCCTCCTCCCAG AGAAGNGGTCCCTCGGCCCCTGNTGTCCCANAGGNTACTATTACTGNGCCNGCAACCGGCAACCGATATC NATTTTGNCATTGGCCTTCAACAATAATTA

16464.2.edit

AGCGTGGTTCGCGGCCGANGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTTC
TTCATCAGNGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGGCCCATGAGATGGTTG
TCTGAGAGAGAGCTTCTTGNCCTGTCTTTTTCCTTCCAATCAGGGGCTCGCTCTTCTGATTATTCTTCAGGGCA
ATGACATAAATTGTATATTCGGGTCCCGGNTCCAGGCCAGTAATAGTANCCTCTGTGACACCAGGGCGGNGCCG
AGGGACCACTTCTCTGGGAGGAGACCCAGGCTTCTCATACTTGATGATGATGAACCGGTAATCCTGGCACGTGGCG
GCTGCCATGATACCAGCAAGGAAATTGGGGTGTGGCCAGGAAACGCAGGTTGGATGGNGCATCAATGGCAGT
GGAGGCCGTCGATGACCACAGGGGGAGCTCCGACATTGTCATTCAAGGTG

16465.1.edit

AGCGTGGNCGCGGCCGAGGTGCAGCGCGGGCTGTGCCACCTTCTGCTCTCTGCCCAACGATAAGGAGGGTNCCTGCCCCAGGAGAACATTAACTNTCCCCAGCTCGGCCTCTGCCGG

16465.2.edit

TCGAGCGGCCGCCCGGGCAGGTTTTTTTTTGCTGAAAGTGGNTACTTTATTGGNTGGAAAGGGAGAAGCTGTGG
TCAGCCCAAGAGGGAATACAGAGNCCCGAAAAAGGGGAGGGCAGGTGGGCTGGAACCAGACCAGGCCAGGCCAGGCA
GAAACTTTCTCTCCTCACTGCTCAGCCTGGTGGTGGTGGCTGGAGCTCANAAATTGGGAGTGACACAGGACACCTTC
CCACAGCCATTGCGGCGGCATTTCATCTGGCCAGGACACTGGCTGTCCACCTGGCACTGGTCCCGACAGAAGCC
CGAGCTGGGGAAAGTTAATGTTCACCTGGGGGCAGGAACCCTCCTTATCATTGNGCAGAGAGCAGAAGGTGGCA
CAGCCCGCGCTGCACCTCGGCCGCGACCACGCT

16466.2.edit

TCGAGCGCCCCGGGCAGGTCCACCATAAGTCCTGATACAACCACGGATGAGCTGTCAGGAGCAAGGTTGAT
TTCTTTCATTGGTCCGGNCTTCTCCTTGGGGGGNCACCCGCACTCGATATCCAGTGAGCTGAACATTGGGTGGCG
TCCACTGGGCGCTCAGGCT

16467.2.edit

TCGAGCGGTTCGCCCGGGCAGGTCCACCCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGA
TTACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGCGGTCCCTCGGCCCCGCCCTGGT
GTCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGNCCTGAAGAATAA
TCANNAANAGCGANCCCCTGATTGGAAGGA

Fig. 15DD

65/101 01_16469.edit

02 16469.edit

03 16470.edit

04 16470.edit

TCGAGCGCCCCGGGCAGGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTT CTTCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGGCCCATGAGATGGTT GTCTGAGAGAGAGGCTTCTTGTCCTACATTCGGCGGGTATGGTCTTGGCCTATGCCTTATGGGGGTGGCCGTTGT GGGCGGTGTGGTCCGCCTAAAACCATGTTCCTCAAAGATCATTTGTTGCCCAACACTGGGTTGCTGACCAGAAG TGCCAGGAAGCTGAATACCATTTCACCTCGGCCGCGACCACGCTA

05 16471.edit

Fig. 15EE

66/101 06 16471.edit

AGCGTGGTCGCGGCCGAGGTCTGCTGCTTCAGCGAAGGGTTTCTGGCATAACCAATGATAAGGCTGCCAAAGAC
TGTTCCAATACCAGCACCAGAACCAGCCACTCCTACTGTTGCAGCACCTGCACCAATAAATTTGGCAGCAGTAT
CAATGTCTCTGCTGATTGCACTGGTCTGAAACTCCCTTTGGATTAGCTGAGACACACCATTCTGGGCCCTGATT
TTCCTAAGATAGAACTCCAACTCTTTGCCCTCTAGCACATAGCCATCTGCTCGGTCACACTGTCCCGGCCTTGA
AGCGATGCACGCAAGAAGCTTGCCCTGCTGGAACTGCTCCTCCAGGAGACTGCTGATTTTTGGCATTCTTTTTCC
TTTCATCATATTTCTTCTGAATTTTTTTTAGATCGTTTTTTTGTTTAAAATCTCTTCTTCCTCAGGAGTCAGCTTG
GCCCCCGCCGCATCCACACAGTCCGTGTGCGGGGAGGTAACAAGAAATACCGTGCCCTGAGGTTGGACGTGGGG
AATTTCTCCTGGGGCTCAGAGTGGTGTACTCGTAAAACAAGGATCATCGATGGTGNCTACAATGCATCTAATAA
CGAGCTGGGTCGGACCCAAAGAACCTGGNGAANAAATGGATCGNCTCATCGACAGGACACCGTACCCGACAGGG
GNACGANTCCCACTATGCGCTTGCCCCTGGGCCGCAANAAAGGAAAACTGCCCGGGCGGCCNTCGAAAGCCCAA
TTNTGGAAAAAATCCATCACACTGGGNGGCCNGTCGAGCATGCATNTANAGGGGCCCCATTCCCCCTNANN

07 16472.edit

TCGAGCGGCCGCCCGGGCAGGTCCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAG ACTGGTGAGACCTGCGTGTACCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAA GGACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCG ACCCTGCCGATGTGGACCTCGGCCGCGACCACGCT

08 16472.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA GCCTTGGTTGGGGACCTGCCCGGGCGGCCGCTCGA

09 16473.edit

Fig. 15FF

67/101 11 16474.edit

12 16474.edit

13 16475.edit

TCGAGCGCCCCCGGGCAGGTCTGGTCCAGGATAGCCTGCGAGTCCTCCTACTGCTACTCCAGACTTGACATC
ATATGAATCATACTGGGGAGAATAGTTCTGAGGACCAGTAGGGCATGATTCACAGATTCCAGGGGGGCCAGGAG
AACCAGGGGACCCTGGTTGTCCTGGAATACCAGGGTCACCATTTCTCCCAGGAATACCAGGAGGCCTGGATCT
CCCTTGGGGCCTTGAGGTCCTTGACCATTAGGAGGGCGAGTAGGAGCAGTTGGAGGCTGTGGGCAAACTGCACA
ACATTCTCCAAATGGAATTTCTGGGTTGGGGCAGTCTAATTCTTGATCCGTCACATATTATGTCATCGCAGAGA
ACGGATCCTGAGTCACAGACACATATTTTGGCATGGTTCTGGCTTCCAGACATCTCTATCCGNCATAGGACTGAC
CAAGATGGGAACATCCTCCTTCAACAAGCTTNCTGTTGTGCCAAAAATAATAGTGGGATGAAGCAGACCGAGAA
GTANCCAGCTCCCCTTTTTTGCACAAAGCNTCATCATGTCTAAATATCAGACATGAGACTTCTTTGGGCAAAAAA
GGAGAAAAAGAAAAAGCAGTTCAAAGTANCCNCCATCAAGTTGGTTCCTTTGCCCNTTCAGCACCCGGGCCCCGT
TATAAAACACCTNGGGCCGGACCCCCCTT

Fig. 15GG

68/101 14_16475.edit

15_16476.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGC
TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA
CTGGGCTGAGTGGGGTACACCGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA
GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGGTCACGGCAGGTGC
GGGCGGGGTTCTTGCGGCTCCCCTCTGGGCTCCGGATGTTCTCCATCTGCTGGCTCAGGCTCTTGAGGGTGGTC
TCCACCTCGAGGTCACGGAACCACATTGGCATCATCAGCCCGGTAGTAGCCGCCACCATCGTGAGCCTT
CTCTTGANGTGGCTGGGGCAGGAACTGAAGTCGAAACCAGCGCTGGGAGGACCAGAGACCAAAAGGTCCAGC
AAGGGCCCGGGGGGGACCAACAGGACCAGCATCACCAAGTGCGACCCGCGAGAACCTGCCCGGCCGNCCGCTCC
AA

16 16476.edit

Fig. 15HH

69/101 17 16477.edit

18 16477.edit

AGCGTGGTTNGCGGCCGAGGTCTGGGCCAGGGGCACCAACACGTCCTCTCTCACCAGGAAGCCCACGGGCTCCT GTTTGACCTGGAGTTCCATTTTCACCAGGGGCACCAGGTTCACCCTTCACACCAGGAGCACCGGGCTGTCCCTT CAATCCATNCAGACCATTGTGNCCCCTAATGCCTTTGAAGCCAGGAAGTCCAGGAGTTCCAGGGAAACCACCGA GCACCCTGTGGTCCAACAACTCCTCTCTCACCAGGTCGTCCGGGTTTTCCAGGGTGACCATCTTCACCAGCCTT GCCAGGAGGACCAGCAGCACCAGCGTTACCAACCTGCCCGGGCGGCCGCTCGA

21 16479.edit

TCGAGCGCCCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT TGTCATGGCACCACTCTGAAATCACACCATCTGAAATGACCACTTCCCAAAGCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACATTCGTTCCCACTCTCCCAACGGCATAATGGGAAACCTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCGACCACG CT

22 16479.edit

Fig. 15II

70/101 24 16480.edit

TCGAGCGNNCGCCCGGGCAGGTCCAGTAGTGCCTTCGGGACTGGGTTCACCCCCAGGTCTGCGGCAGTTGTCAC
AGCGCCAGCCCCGCTGGCCTCCAAAGCATGTGCAGGAGCAAATGGCACCGAGATATTCCTTCTGCCACTGTTCT
CCTACGTGGTATGTCTTCCCATCATCGTAACACGTTGCCTCATGAGGGTCACACTTGAATTCTCCTTTTCCGTT
CCCAAGACATGTGCAGCTCATTTGGCTGGCTCTATAGTTTGGGGAAAGTTTGTTGAAACTGTGCCACTGACCTT
TACTTCCTCCTTCTCTACTGGAGCTTTCGTACCTTCCACTTCTGCTGTTGGTAAAATGGTGGATCTTCTATCAA
TTTCATTGACAGTACCCACTTCTCCCCAAACATCCAGGGAAAATAGTGATTTCAGTGGTGACTTTAAAAGAATA
ATGGGGCAGAAATAAGGGGCTTTTCCACAGGTTTTCCTTTGGAGGAAGATTTCAGTGGTGACTTTAAAAGAATA
CTCAACAGTGTCTTCATCCCCATAGCAAAAGAAGAAACNGTAAATGATGGAANGCTTCTGGAGATGCCNNCATT
TAAGGGACNCCCAGAACTTCACCATCTACAGGACCTACTTCAGTTTACANNAAGNCACATANTCTGACTCANAA
AGGACCCAAGTAGCNCCATGGNCAGCACTTTNAGCCTTTCCCCTGGGGAAAANNTTACNTTCTTAAANCCTNGG
CCNNGACCCCCTTAAGNCCAAATTNTGGAAAAANTTCCNTNCNNCTGGGGGGCNGTTCNACATGCNTTTNAAGGG
CCCAATTNCCCCNT

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26 16481.edit

27 16482.edit

TCGAGCGCCCCGGGCAGGTTGAATGGCTCCTCGCTGACCACCCCGGTGCTGGTGGTGGTACAGAGCTCCG ATGGGTGAAACCATTGACATAGAGACTGTCCCTGTCCAGGGTGTAGGGGCCCAGCTCAGTGATGCCGTGGGTCA GCTGGCTCAGCTTCCAGTACAGCCGCTCTCTGTCCAGTCCAGGGCTTTTGGGGTCAGGACGATGGGTGCAGACA GCATCCACTCTGGTGGCTGCCCCATCCTTCTCAGGCCTGAGCAAGGTCAGTCTGCAACCAGAGTACAGAGAGCT GACACTGGTGTTCTTGAACAAGGGCATAAGCAGACCCTGAAGGACACCTCGGCCGCCGACCACGCT

Fig. 15JJ

71/101 28_16482.edit

29 16483.edit

31 16484.edit

37 16487.edit

Fig. 15KK

72/101

38 16487.edit

39 16488.edit

NGGNNGGTCCGGNCNGNCAGGACCACTCNTCTTCGAAATA

41 16489.edit

42 16489.edit

45 16491.edit

TCGAGCGGCCGCCCGGGCAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCTCGGCCGCGACCACGCT

Fig. 15LL

73/101 46 16491.edit

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Fig. 15MM

74/101 49 16493.edit

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TCGAGCGGCCGCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC
TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCCACCACG
CT

59 16498.edit

TCGAGCGCCCCCGGGCAGGTCCACCATAAGTCCTGATACAACCACGGATGAGCTGTCAGGAGCAAGGTTGAT
TTCTTTCATTGGTCCGGTCTTCTCCTTGGGGGTCACCCGCACTCGATATCCAGTGAGCTGAACATTGGGTGGTG
TCCACTGGGCGCTCAGGCTTGTGGGTGTGACCTGAGTGAACCTTCAGGTCAGTTGGTGCAGGAATAGTGGTTACT
GCAGTCTGAACCAGAGGCTGACTCTCTCCGCTTGGATTCTGAGCATAGACACTAACCACATACTCCACTGTGGG
CTGCAAGCCTTCAATAGTCATTTCTGTTTGATCTGGACCTGCAGTTTTAGTTTTTGTTGGTCCTGGTCCATTTT
TGGGAGTGGTGGTTACTCTGTAACCAGTAACAGGGGAACTTGAAGGCAGCCACTTGACACTAATGCTGTTGTCC
TGAACATCGGTCACTTGCATCTGGGATGGTTTGNCAATTTCTGTTCGGTAATTAATGGAAATTGGCTTGCTGCT
TGCGGGGCTGTCTCCACGGCCAGTGACAGCATACACAGNGATGGNATNATCAACTCCAAGTTTAAGGCCCTGAT
GGTAACTTTAAACTTGCTCCCAGCCAGNGAACTTCCGGACAGGGTATTTCTTCTGTTTTCCGAAAGNGANCCT
GGAATNNTCTCCTTGGANCAGAAGGANCNTCCAAAACTTGGGCCGGAACCCCTT

Fig. 15NN

75/101 60 16473.edit

60 16498.edit

61 16499.edit

AGCGTGGTCGCGGCCGAGGTCNAGGA

62 16483.edit

TCGAGCGGCCGCCCGGGCAGGTCCACCACCCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGGAATATACAATTTATGTCATTGCCCTGAAGAATAAT CAGAAGAGCGAGCCCCTGATTGGAAGGAAAAAGACAGACGAGCTTCCCCAACTGGTAACCCTTCCACACCCCAA TCTTCATGGACCAGAGATCTTGGATGTTCCTTCCACAGGTTCAAAAGACCCCTTTCGTCACCCCCCCAACTGGAAATGGTATTCAGCTTCCTGGCACTTCTGGTCAGCAACCCAGTGTTGGGCAACAAATGATCTTTGAG GAACATGGTTTTAGGCGGACCACACCGCCCCACAACGGGCACCCCCATAAGGNATAGGCCAAGACCATACCCCGC CGAATGTAGGACAAGAAGCTCTNTCTCAACAACCATCTCATGGGCCCCATTCCAGGACACTTCTGAGTACATCA TTTCATGTCATCCTGGTGGGCACCTTCTACAGNGCCA CTTCTGACAGGACACTTCTGAGTACACCACCCTTACAGTTCAGGGTTCCTGGAACTTCTACCAGNGCCA CTTCTGACAGGACACTTCTGAGGACCACCCCT

Fig. 1500

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76/101 63 16500.edit

AGCGTGGTCGCGGCCGAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCATTG
TCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCCAAAGCCTAAGCACTGGCACAACAGTTTAAA
GCCTGATTCAGACATTCGTTCCCACTCATCTCCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGAGT
CATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCCTC
TGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTGCCCGGGCGCCCCGCT
CGA

64_16493.edit

64 16500.edit

Fig. 15PP

77/101

16501.edit

16501.2.edit

GAGGACTGGCTCAGCTCCCAGTATAGCCGCTCTCTGTCCAGTCCAGGACCAGTGGGATCAAGGCGGAGGGTGCA GATGGCGTCCACTCCAGTGGCTGCCCCATGTTTCTCAAGTCTGAGCAAAGNCAGTCTGCAGCCAGAGTACAGAG GGCCAACACTGGTGCTCTTGAACAGGGACCTGAGCAGGCCCTGAAGGACCCTCTCCGTGGTGTTGAACTTCCTG GAGCCAGGGTGCTGCATGTTCTCCTCATACCGCAGGTTGTTGATGGTGAAGTTCAGTGTGAATGGCTCCTCGCT GACCACCC

16502.1.edit

16502.2.edit

TCGAGCGGCCGCCCGGGCAGGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTT
CTTCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGGCCCATGAGATGGTT
GTCTGAGAGAGAGAGCTTCTTGTCCTACATTCGGCGGGTATGGTCTTGGCCTATGCCTTATGGGGGTGGCCGTTGT
GGGCGGTGTGGTCCGCCTAAAACCATGTTCCTCAAAGATCATTTGTTGCCCAACACTGGGTTGCTGACCAGAAG
TGCCAGGAAGCTGAATACCATTTCCAGTGTCATACCCAGGGNGGGTGACCAAAGGGGGTCNTTTNGACCTGGNG
AAAGGAACCATCCAAAANCTCTGNCCCATG

Fig. 15QQ

78/101 16503.1.edit

16503.2.edit

AAGCGGCCGCCGGGCAGGNNCAGNAGTGCCTTCGGGACTGGGNTCACCCCCAGGTCTGCGGCAGTTGTCACAG
CGCCAGCCCCGCTGGCCTCCAAAGCATGTGCAGGAGCAAATGGCACCGAGATATTCCTTCTGCCACTGTTCTCC
TACGTGGTATGTCTTCCCATCATCGTAACACGTTGCCTCATGAGGGTCACACTTGAATTCTCCTTTTCCGTTCC
CAAGACATGTGCAGCTCATTTGGCTGGCTCTATAGTTTGGGGAAAGTTTGTTGAAACTGTGCCACTGACCTTTA
CTTCCTCCTTCTCTACTGGAGCTTTCCGTACCTTCCACTTCTGCTGNTGGNAAAAAGGGNGGAACNTCTTATCA
ATTTCATTGGACAGTANCCCNCTTTCTNCCCAAAACATNCAAGGGAAAATATTGATTNCNAGAGCGGATTAAGG
AACAACCCNAATTATGGGGGCCCAGAAATAAAAGGGGGCTTTTTCCACAGGTNTTTTTCCT

16504.1.edit

TCGAGCGGCCGCCCGGGCAGGTCTGCAGGCTATTGTAAGTGTTCTGAGCACATATGAGATAACCTGGGCCAAGC
TATGATGTTCGATACGTTAGGTGTATTAAATGCACTTTTGACTGCCATCTCAGTGGATGACAGCCTTCTCACTG
ACAGCAGAGATCTTCCTCACTGTGCCAGTGGGCAGGAGAAAGAGCATGCTGCGACTGGACCTCGGCCGCCGACCA
CGCT

16504.2.edit

AGCGTGGTCGCGGCCGAGGTCCAGTCGCAGCATGCTCTTTCTCCTGCCCACTGGCACAGTGAGGAAGATCTCTG CTGTCAGTGAGAAGGCTGTCATCCACTGAGATGGCAGTCAAAAGTGCATTTAATACACCTAACGTATCGAACAT CATAGCTTGGCCCAGGTTATCTCATATGTGCTCAGAACACTTACAATAGCCTGCAGACCTGCCCGGGCGGCCGC TCGA

Fig. 15RR

79/101

16505.1.edit

CGAGCGGCCGCCGGGCAGGTCCAGACTCCAATCCAGAGAACCACCAAGCCAGATGTCAGAAGCTACACCATCA CAGGTTTACAACCAGGCACTGACTACAAGATCTACCTGTACACCTTGAATGACAATGCTCGGAGCTCCCCTGTG GTCATCGACGCCTCCACTGCCATTGATGCACCATCCAACCTGCGTTTCCTGGCCACCACCACCCCAATTCCTTGCT GGTATCATGGCAGCCGCCACGTGCCAGGATTACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCA GAGAAGTGGTCCCTCGGCCCCCGCCCTGGTGNCACAGAAGCTACTATTACTGGCCTGGAACCGGGAACCGAATAT ACAATTTATGTCATTGCCCTGAAGAAATAATCANAAGAGCGAGCCCCTGATTGGAAGG

16505.2.edit

16506.1.edit

16506.2.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG
TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA
CTGGGCTGAGTGGGGTACACCGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA
GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGTGC
GGGCGGGGTTCTTGCGGCTGCCCTCTGGGCTCCGGATGTTCTCGATCTGCTGGCTCAAGCTCTTGAAGGGTGGT
GTCCACCTCGAGGTCACGGACCGCAAACCTGCCCGGGCGCCGCTCGA

Fig. 15SS

80/101

16507.1.edit

AGCGTGGTCGCGGCCGAGGTCAAGAACCCCGCCCGCACCTGCCGTGACCTCAAGATGTGCCACTCTGACTGGAA GAGTGGAGAGACTGGAGATGTGACACCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAGA CTGGTGAGACCTGCGTGTACCCCCACTCAGCCCAAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCCAAG GACAAGAGCATGTCTGGTTCGGCGAGAGAACCCCAAGTTCCAGTTCGAGTATGGCGGCCAGGGCTCCGA CCCTGCCGATGTGGACCTGCCGNGCCGGNCCGCTCGAAAAGCCCNAATTTCCAGNCACACTTGGCCGGCCGTT ACTACTG

16507.2.edit

TCGAGCGGCCGCCCGGGCAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCTCGGCCGCGACCACGCT

16508.1.edit

16508.2.edit

Fig. 15TT

81/101

16509.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAAGTAACCACCACTCCCAAAAATGGACCAGGA
CCAACAAAAACTAAAACTGCAGGTCCAGATCAAACAGAAAATGGACTATTGAAGGCTTGCAGCCCACAGTGGAA
GTATGTGGNTAGGNGTCTATGCTCAGAATCCCAAGCCGGAGAAAGTCAGCCTTCTGGTTTAGACTGCAGTAACC
AACATTGATCGCCCTAAAGGACTGGNCATTCACTTGGATGGTGGATGTCCAATTC

16509.2.edit

16510.1.edit

16510.2.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGTAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAGTAACCACCACTCCCAAAAATTGGGACCAGGA
CCAACAAAAAACTAAAACTGCANGGTCCAGATCAAACAGAAATGACTATTGAAGGCTTTCAGACT
TATGTGGGTTAGTGTCTATGCTCAGAATNCCAAGCGGAGAGAGTCAGCCTCTGGTTCAGACT

Fig. 15UU

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16511.1.edit

16511.2.edit

AGCGTGGTCGCGGCCGAGGTCTGTAGCTTCTGTGGGACTTCCACTGCTCAGGCGTCAGGCTCAGGTAGCTGCTG
GCCGCGTACTTGTTGTTGCTTTGNTTGGAGGGTGTGGTGGTCTCCACTCCCGCCTTGACGGGGCTGCTATCTGC
CTTCCAGGCCACTGTCACGGCTCCCGGGTAGAAGTCACTTATGAGACACACCCAGTGTGGCCTTGTTGGCTTGAA
GCTCCTCAGAGGAGGGTGGGAACAGAGTGACCGAGGGGGCAGCCTTGGGCTGACCTAGGACGGTCAGCTTGGTC
CCTCCGCCGAACACCCAATTGTTGTTGCCTGCATATGAGCTGCAGTAATAATCAGCCTCATCCTCAGCCTGGAG
CCCAGAGACNGTCAAGGGAGGCCCGTGTTTGCCAAGACTTGGAAGCCAGANAAGCGATCAGGGACCCCTGAGGG
CCGCTTTACNGACCTCAAAAAATCATGAATTTGGGGGGCCCTTTGCCTGGGNGTTGGTTAGTNACCAGNAAAACA
AAATTTCATAAAGCACCAACGTCACTGCTGGTTTCCAGTGCANGAANATGGTGAACTGAANTGTCC

16512.1.edit

16512.2.edit

TCGAGCGCCCCCGGGCAGGTCCATACAGGGCTGTTGCCCAGGCCCTAGAGGNCATTCCTTGTACCCTGATCC AGAACTGTGGGACCAGCACCACCCAGCACACCCCAGGAGAACTGTGAGACC TGGGGTGTAAATGGNGAGACGGGTACTTTGGTGGACATGAAGGAACTGGGGCATATGGGAGCCATTGGCTGNGAA GCTGCANACTTATAAGACAGCAGTGGAGACGGCAGTTCTGCTACTGCGAATTGATGACATCGTTTCAGGCCACA AAAAGAAAGGCGATGACCANAGCCGGCAAGGCGGGGGCTTCCTGATGCTGGACCTCGGCCGCCGACCACGCTT

Fig. 15VV

83/101

16514.1.edit

AGCGTGGTCGCGGCCGAGGTCCACTAGAGGTCTGTGTGCCATTGCCCAGGCAGAGTCTCTGCGTTACAAACTCC
TAGGAGGGCTTGCTGTGCGGAGGGCCTGCTATGGTGTGCTGCGGTTCATCATGGAGAGTTGGGGGCCAAAGGCTGC
GAGGTTGTGGTGTCTGGGAAACTCCGAGGACAGAGGGCTAAATCCATGAAGTTTGTGGATGGCCTGATGATCCA
CAGCGGAGACCCTGTTAACTACTACGTTGACACTGCTGTGCGCCACGTGTTGCTCANACAGGGTGTGCTGGGCA
TCAAGGTGAAGATCATGCTGCCCTGGGACCCANCTGGCAAAAATGGCCCTTAAAAAACCCCTTGCCNTGACCACG
TGAACCATTTGTGNGAACCCCAAGATGAANATACTTGCCCACCACCCCCCATTC

16514.2.edit

16515.1.edit

16515.2.edit

TCGAGCGGCCGCCCGGGCAGGTCTGGGCCAGGGGCACCAACACGTCCTCTCACCAGGAAGCCCACGGGCTCC
TGTTTGACCTGGAGTTCCATTTTCACCAGGGGCACCAGGTTCACCCTTCACACCAGGAGCACCGGGCTGTCCCT
TCAATCCATCCAGACCATTGTGNCCCCTAATGCCTTTGAAGCCAGGAAGTCCAGGAGTTCCAGGGAAACCACGA
GCACCCTGTGGTCCAACAACTCCTCTCTCACCAGGTCGTCCGGGTTTTCCAGGGTGACCATCTTCACCAGCCTT
GCCAGGAGGGCCAGACCTCGGCCGCGACCACGCT

Fig. 15WW

84/101

16516.1.edit

ANCGTGGTCGCGGCCGAGGTCCTCACCAGAGGTGNCACCTACAACATCATAGTGGAGGCACTGAAAGACCANCA GAGGCATAAGGTTCGGGAAGAGG

16516.2.edit

16517.1.edit

16518.1.edit

AGCGTGGTCGCGGCCGAGGTCTGAGGTTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGT
TCAACTGGTACGTGGACGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACG
TACCGGGNGGTCAGCGTCCTCACCGTCCTGCACCAGAATTGGTTGAATGGCAAGGAGTACAAGNGCAAGGTTTC
CAACAAAGCCNTCCCAGCCCCCNTCGAAAAAACCATTTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGT
ACACCCTGCCCCCATCCCGGGAGGAAAAGANCAANAACCNGGTTCAGCCTTAACTTGCTTGGTCNAANGCTTTT
TATCCCAACGNACTTCCCCCNTGGAANTGGGAAAAACCAATGGGCCAANCCGAAAAACAATTACAANAACCCC

16518.2.edit

Fig. 15XX

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16519.1.edit

AGCGTGGTCGCGGACGANGTCCTGTCAGAGTGGNACTGGTAGAAGTTCCANGAACCCTGAACTGTAAGGGTTCT TCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGNGNCCTGGAATGGGGCCCATGANATGGTTGC C

16519.2.edit

TCGAGCGCCCCCGGGCAGGTCCACCACCCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGGAATATACAATTTATGTCATTGCCCTGAAGAATAAT CAGAAGAGCGAGCCCCTGATTGGAAGGAAAAAGACAGACGAGCTTCCCCAACTGGTAACCCTTCCACACCCCAA TCTTCATGGACCAGAGATCTTGGATGTTCCTTCCACAGTTCAAAAGACCCCTTTCGGCACCCCCCTGGGTATG AACCTGGGAAAANGGNANTTAANCTTTCCTGGCA

16520.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGGTNCCCTGGTACTGGGTTACAGANTAACCACCACTCCCAAAAATGGACCAGGA
ACCACAAAAACTTAAACTGCAGGGTCCAGATCAAAACAGAAATGACTATTGAANGCTTGCAGCCCACAGTGGGA
GTATGNGGGTAGTGNCTATGCTTCAGAATCCAAGCGGAAAAANGTCAAGCCTTNTGGGTTCAA

16520.2.edit

TCGAGCGGCCCGGGCAGGTCCTTGCAGCTCTGCAGTGTCTTCTTCACCATCAGGTGCAGGGAATAGCTCAT GGATTCCATCCTCAGGGCTCGAGTAGGTCACCTGTACCTGGAAACTTGCCCCTGTGGGCTTTCCCAAGCAATT TTGATGGAATCGACATCCACATCAGTGAATGCCAGTCCTTTAGGGCGATCAATGTTGGTTACTGCAGNCTGAAC CAGAGGCTGACTCTCTCCGCTTGGATTCTGAGCATAGACACTAACCACATACTCCACTGTGGGCTGCAANCCTT CAATAANNCATTTCTGTTTGATCTGGACC

16521.2.edit

TCGAGCGGCCGGGCAGGTCTGGTGGGGTCCTGGCACACGCACATGGGGGNGTTGNTCTNATCCAGCTGCC CAGCCCCCATTGGCGAGTTTGAGAAGGTGTGCAGCAATGACAACAANACCTTCGACTCTTCCTGCCACTTCTTT GCCACAAAGTGCACCCTGGAGGGCACCAAGAAGGGCCACAAGCTCCACCTGGACTACATCGGGCCTTGCAAATA CATCCCCCCTTGCCTGGACTCTGAGCTGACCGAATTCCCCCTTGCGCATGCGGGACTGGCTCAAGAACCGTCCT GGCACCCTTGTATGANAGGGATGAAGACACNACCC

Fig. 15YY

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16522.1.edit

16522.2.edit

TCGAGCGCCCCCGGGCAGGTTTGGAAGGGGGATGCGGGGGAAGAGAAGACTGACGGTCCCCCCAGGAGTTC AGGTGCTGGGCACGGTGGGCATGTTGTGAGTTTTGTCACAAGATTTTGGCCTCAACTCTCTTGTCCACCTTGGTGT TGCTGGGCTTGTGATCTACGTTGCAGGTGTAGGTCTGGGNGCCGAAGTTGCTGGAGGGCACGGTCACCACGCTG CTGAGGGAGTAGAGTCCTGAGGACTGTANGACAGACCTCGGCCGNGACCACGCTAAGCCGAATTCTGCAGATAT CCATCACACTGGCGGCCGCTCCGAGCATGCATTTTAGAGG

16523.1.edit

AGCGTGGNCGCGGACGANGACAACAACCCC

16523.2.edit

TCGAGCGGCCGCCCGGGCAGGNCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTTGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGNACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCT

16524.1.edit

AGCGTGGTCGCGGCCGAGGTCCAGCCTGGAGATAANGGTGAAGGTGGTGCCCCCGGACTTCCAGGTATAGCTGG ACCTCGTGGTAGCCCTGGTGAGAGAGGGGGCCCCCCCAGGACCTGCTGGTTTCCCTGGTGCTCCTGGAC AGAATGGTGAACCTGGNGGTAAAGGAGAAAGAGGGGCTCCGGNTGANAAAGGTGAAGGAGGCCCTCCTGNATTG GCAGGGGCCCCANGACTTAGAGGTGGAGCTGGCCCCCCTGGCCCCCGAAGGAGGAAAGGGTGCTGCTGGTCCTCC TGGGCCACCTGG

Fig. 15ZZ

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16524.2.edit

TCGAGCGCCCCGGGCAGGTCTGGGCCAGGAGGACCAATAGGACCAGTAGGACCCCTTGGGCCATCTTTCCC
TGGGACACCATCAGCACCTGGACCGCCTGGTTCACCCTTGTCACCCTTTGGACCAGGACTTCCAAGACCTCCTC
TTTCTCCAGGCATTCCTTGCAGACCAGGAGTACCANCAGCACCAGGTGGCCCAGGAGGACCAGCACCCTTT
CCTCCTTCGGGACCAGGGGGACCAGCTCCACCTCTAAGTCCTGGGGCCCCTGCCAATCCAGGAGGGCCTCCTTC
ACCTTTCTCACCCGGAGCCCCTCTTTCT

16526.1.edit

16526.2.edit

ATGCGNGGTCGCGGCCGANGACCANCTCTGGCTCATACTTGACTCTAAAGNCNTCACCAGNANTTACGGNCATT GCCAATCTGCAGAACGATGCGGGCATTGTCCGCANTATTTGCGAAGATCTGAGCCCTCAGGNCCTCGATGATCT TGAAGTAANGGCTCCAGTCTCTGACCTGGGGTCCCTTCTTCTCCAAGTGCTCCCGGATTTTGCTCTCCAGCCTC CGGTTCTCCGGTCTCCAAGNCTTCTCACTCTGTCCAGGAAAAGAGGCCAGGCGGNCGATCAGGGCTTTTGCATGG ACT

16527.1.edit

16527.2.edit

TCGAGCGCCCCGGGCAGGTCTGCCAACACCAAGATTGGCCCCCGCCGCATCCACACAGTTNGTGTGCGGGG AGGTAACAAGAAATACCGTGCCCTGAGGNTGGACGNGGGGGAATTTCTCCTGGGGCTCAGAGTGTTGTACTCGTA AAACAAGGATCATCGATGTTGTCTACAATGCATCTAATAACGAGCTGGTTCGTACCAAGACCCTGGTGAAGAAT TGCATCGTGCTCATNGACAGCACACCGTACCGACAGTGGGTACCGAAGTCCCACTATGCNCCT

Fig. 15AAA

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16528.1.edit

TCGAGCGCCCCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGCCCTGAAG

16528.2.edit

AGCGTGNTCNCGGCCGAGGATGGGGAAGCTCGNCTGTCTTTTTTCCTTCCAATCAGGGGCTNNNTCTTCTGATTA
TTCTTCAGGGCAANGACATAAATTGTATATTCGGNTCCCGGTTCCAGNCCAGTAATAGTAGCCTCTGTGACACC
AGGGCGGGGCCGAGGGACCACTTCTCTGGGAGGAGACCCAGGCTTCTCATACTTGATGATGAAGCCGGTAATCC
TGGCACGTGGGCGGCTGCCATGATACCACCAANGAATTGGGTGTGGTGGACCTGCCCGGGCGGCCGCTCGAAA
ANCCGAATTCNTGCAAGAATATCCATCACACTTGGGCGGCCGNTCGAACCATGCATCNTAAAAGGGCCCCAAT
TTCCCCCCTATTAGGNGAAGCCNCATTTAACAAATTCCACTTGG

16529.1.edit

16529.2.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG
TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA
CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA
GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAAGTGGCACATCTTGAGGTCACGGCAGGGT
GCGGGCGGGGTTCTTGCGGGCTGCCCTTCTGGGCTCCCGGAATGTTCTNNGAACTTGCTGG

Fig. 15BBB

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16530.1.edit

16530.2.edit

16531.1.edit

TCGAGCGCCCCCGGGCAGGTGTTTCAGAGGTTCCAAGGTCCACTGTGGAGGTCCCAGGAGTGCTGGTGGGGCACAGAGGTCCGAGGGTGAAACCATTGACATAGAGACTGTTCCTGTCCAGGGTGTAGGGGCCCAGCTCTTTGATGCCATTGGCCAGTTGGCTCAGCTCCCAGTACAGCCGCTCTCTGTTGAGTCCAGGGCTTTTGGGGTCAAGATGATGCAGTCCAGTTCCACTCCAGTGGCTCCCATCCTTCTCGGACCTGAGAGAGGTCAGTCTGCAGCCAGAGTCAGAGAGGGCCAACACTGGTGTTCTTTGAATA

16531.2.edit

16532.1.edit

Fig. 15CCC

90/101 01_16558.3.edit

AGCGTGGTCGCGGCCGAGGTGAGCCACAGGTGACCGGGGCTGAAGCTGGGGCTGCTGGNCCTGCTGGTCCTG

02_16558.4.edit

CAGCNGCTCCNACGGGGCCTGNGGGACCAACACACCGTTTTCACCCTTAGGCCCCTTTTTTCTCCT TTAGCACCAGGTTGACCAGCAGCNCCANCAGGACCAGCAGCACCAGCAGCCCGGCCAGCAGCCCCACCTTCACCACG TTCACCAGGGCTTCCCCGAGGACCAGCAGGACCAGCAGCAGCAGCCCCAGCTTCGCCCCGGTCACCTGTGG CTCACCTCGGCCGCGACCACGCT

03 16535.1.edit

TCGAGCGGTCGCCCGGGCAGGTCCACCGGGATAGCCGGGGGTCTGGCAGGAATGGGAGGCATCCAGAACGAGAA GGAGACCATGCAAAGCCTGAACGACCGCCTGGCCTCTTACCTGGACAGAGTGAGGAGCCTGGAGACCGANAACC GGAGGCTGGANAGCAAAATCCGGGAGCACTTGGAGAAGAAGGGACCCCAGGTCAAGAGACTGGAGCCATTACTT CAAGATCATCGAGGGACCTGGAGG

04_16535.2.edit

AGCGNGGTCGCGGCCGAGGTCCAGCTCTGTCTCATACTTGACTCTAAAGTCATCAGCAGCAAGACGGGCATTGT CAATCTGCAGAACGATCGGGGCATTGTCCGCAGTATTTGCGAAGATCTGAGCCCTCAGGTCCTCGATGATCTTG AAGTAATGGCTCCAGTCTCTGACCTGGGGTCCCTTCTTCTCCAAGTGCTCCCGGATTTTGCTCCCAGCCTCCG GTTCTCGGTCTCCAGGCTCCTCACTCTGTCCAGGTAAGAAGGCCCAGGCGGTCGTTCAGGCTTTGCATGGTCTC CTTCTCGGTTCTGGATGCCTCCCATTCCTGCCAGACCC

05 16536.1.edit

TCGAGCGGCCGCCCGGGCAGGTCAGGAAGCACATTGGTCTTAGAGCCACTGCCTCCTGGATTCCACCTGTGCTG
CGGACATCTCCAGGGAGTGCAGAAGGGAAGCAGGTCAAACTGCTCAGATCAGACTAGACTGCTGTTCTCAGTTC
TCACCTGAGCAAGGTCAGTCTGCAGCCAGAGTACAGAGGGCCAACACTGGTGTTCTTGAACAAGGGCTTGAGCA
GACCCTGCAGAACCCTCTTCCGTGGTGTTGAACTTCCTGGAAACCAGGGTGTTGCATGTTTTTCCTCATAATGC
AAGGTTGGTGATGG

Fig. 15DDD

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08_16537.2.edit

Fig. 15EEE

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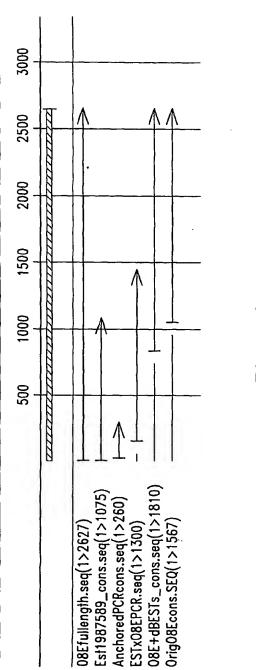


Fig. 16

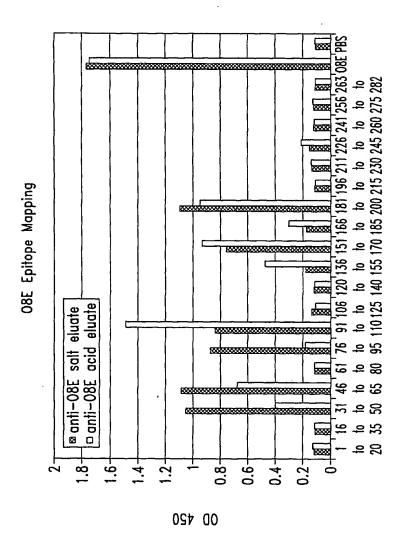
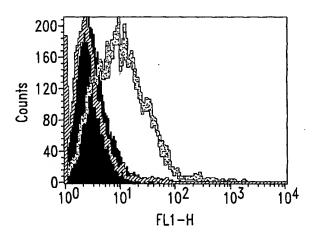


Fig. 17

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08E Surface Expression

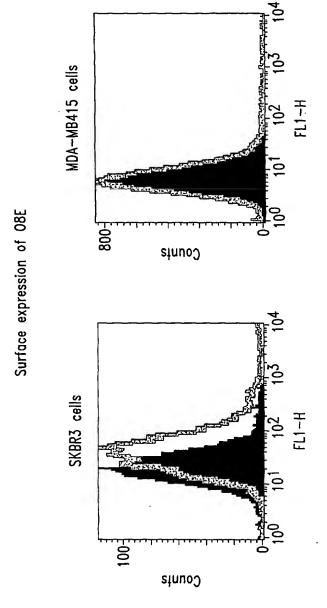


B305D/HEK stained with anti-08E antibody

08E/HEK stained with anti-08E antibody

08E/HEK stained with an irrelevant antibody

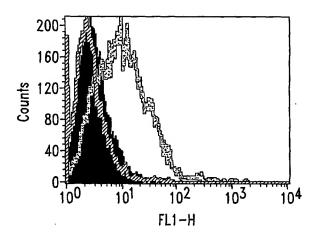
Fig. 18



Black; irrelevant antibody Light gray; anti-08E antibody

Fig. 19

O8E Surface Expression

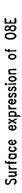


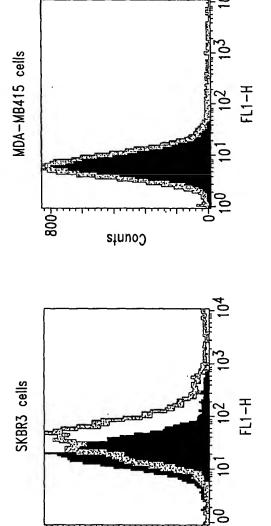
B305D/HEK stained with anti-08E antibody

O8E/HEK stained with anti-08E antibody

O8E/HEK stained with an irrelevant antibody

Fig. 20





Black; Irrelevant antibody Light Grey; Anti-08E antibody

Fig 21

Sinno

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O8E expression in HEK293 Cells (probed with anti-08E rabbit polyclonal sera #2333L)

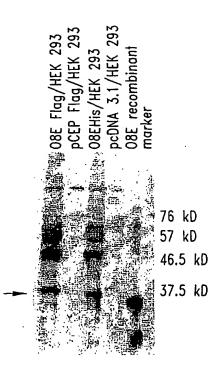


Fig. 22

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08E Rabbits 01212000

						99	// 1	UΊ					
Antibody Dilutions	1:2048000	0.07	0.07	0.07	0.15	0.16	0.16	0.07	0.07	0.07	0.14	0.14	0.14
	1:1024000	0.07	90.0	90.0	0.24	0.23	0.23	0.07	0.07	0.07	0.20	0.20	0.20
	1:512000	0.07	0.07	0.07	0.40	0.40	0.40	0.07	0.07	0.07	0.32	0.35	0.33
	1:256000	0.07	90.0	0.07	99.0	99.0	0.67	0.07	0.07	0.07	0.58	0.58	0.58
	1:128000	0.06	90.0	90.0	1:01	1.00	1.00	0.07	0.07	0.07	0.92	0.88	0.00
	1:64000	0.07	0.07	0.07	1.61	1.57	1.59	0.07	0.07	0.07	14.	1.44	1.43
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	1.1600	0.0	. 0.07	0.07	2.58	2.48	2.53	0:0	0.10	89.	2.30	2.37	2.33
	98: 98:	0.07	0.07	0.07	5.70	5.69	5.69	90.0	0.07	99.	2.48	2.60	2.54
	0 1:4000 1:	0.08	0.07	0.07	2.74	2.74	2.74	90.0	90.0	0.06	2.64	251	2.57
	1.28	0.03	0.08	89.	2.81	277	573	0.07	0.07	0.07	2.75	2.76	5.76
	1:1000	0.13	0.10	0.1	2.92	2.93	2.93	0.03	0.08	0.08	2.73	2.73	2.73
sera sample		Preimmune sera (#2576L):11/10/99	•	Average	α-08E (#2576K):1/11/2000	-	Average	Preimmune sera (#2333L):11/10/99		Average	α-08E (#2333L):1/11/2000		Average
Antigen	on Plate	380	(#632–24)										
			_										

Mg. Z.

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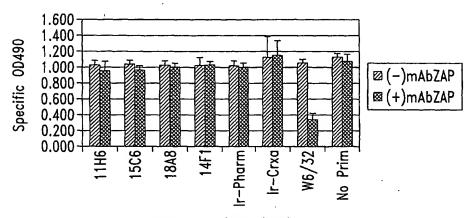
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	1:2048000	90:0	0.07	0.08	0.14	0.14	0.14	0.11	0.11	0.11	0.13	0.13	0.13
	1:1024000	0.07	0.07	0.07	0.20	0.21	0.21	0.15	0.14	0.15	0.19	0.19	0.19
	1:512000	90:0	0.07	90:0	0.33	0.34	0.34	0.22	0.22	0.22	0.29	0.29	0.29
	1:256000	1	0.07	0.07	0.57	0.57	0.57	0.38	0.37	0.37	0.49	0.48	0.49
Dilution	1:128000	0.07	0.07	0.07	0.92	0.94	0.93	0.64	0.62	0.63	0.81	0.82	0.81
Antibody	1:64000	0.07	0.07	0.07	1.39	1.42	14:1	0.99	9.1	9:	1.29	1.30	5.7
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	1:400	0.09	0.03	0.08	2.63	2.64	2.63	2.50	2.38	2.44	2.40	2.61	2.51
	1:2000	0.11	0.10	0.10	2.71	7.68	2.70	2.60	2.48	2.54	2.39	5.66	2.53
	1:1000	0.15	0.14	0.14	2.74	2.72	2.73	7.69	2.59	2.64	2.46	2.65	2.56
Sera Sample		preimmune sera (2576L)		Average	α -08E (2576K):2/8/2000		Average	affinity pure a-08E poly	salt peak 739-87A	Average	affinity pure a-08E poly	acid peak 739-67B	Average
Anfigen	on Plate	08E	#632-24		٠				_				_
	Sera Sample Antibody Dilutions	Sera Sample Antibody Dilutions 1:1000 1:2000 1:4000 1:8000 1:16000 1:32000 1:6000 1:12000 1:1024000	Sera Sample Antibody Dilutions 1:1000 1:2000 1:4000 1:16000 1:32000 1:54000 1:128000 1:256000 1:512000 1:1024000 1:02400 1:02400 1:02400 1:02400 1:02400 1:02400 1:02	Sera Sample 1:1000 1:2000 1:4000 1:8000 1:16000 1:52000 1:128000 1:256000 1:512000 1:1024000 preimmune sera (2576L) 0.15 0.11 0.09 0.08 0.07 0.07 0.07 0.07 0.07 0.07 0.07	Sera Sample Antibody Dilutions 1:1000 1:2000 1:4000 1:8000 1:16000 1:52000 1:12000 1:12000 1:1024000 preimmune sera (2576L) 0.15 0.11 0.09 0.08 0.08 0.07 0.07 0.07 0.07 0.07 0.07	Sera Sample Antibody Dilutions preimmune sera (2576L) 0.15 0.11 0.09 0.08 0.08 0.07 0.07 0.07 0.07 0.07 0.07	Sera Sample Antibody Dilutions preimmune sera (2576L) 0.15 0.11 0.09 0.08 0.08 0.07 0.07 0.07 0.07 0.07 0.07	Sera Sample Antibody Dilutions preimmune sera (2576L) 0.15 0.11 0.09 0.08 0.08 0.07 0.07 0.07 0.07 0.07 0.07	Sera Sample Antibody Dilutions preimmune sera (2576L) 0.15 0.11 0.09 0.08 0.08 0.07 0.07 0.07 0.07 0.07 0.07	Sera Sample Antibody Dilutions preimmune sera (2576L) 0.15 0.11 0.09 0.08 0.08 0.07 0.07 0.07 0.07 0.07 0.07	Sera Sample Antibody Dilutions preimmune sera (2576L) 0.15 0.11 0.09 0.08 0.08 0.07 0.07 0.07 0.07 0.07 0.07	Sera Sample Antibody Dilutions preimmune sera (2576L) 0.15 0.11 0.09 0.08 0.08 0.07 0.07 0.07 0.07 0.07 0.07	Sera Sample 1:1000 1:2000 1:4000 1:8000 1:16000 1:32000 1:64000 1:128000 1:256000 1:512000 1:1024000

Fig. 24

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Anti-08E mAb Binding to 08E Amino Acids 61-80 Induces Ligand Internalization

Hek Internalization of OBE mAbs



Primary Ab (50ng/well)

Hek/08E Internalization of 08E mAbs

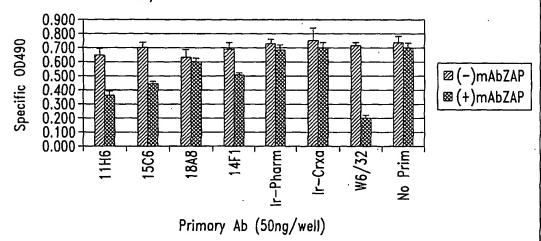


Fig. 25

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6

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cagcagggcc tcatcacact gggctggatt catactcacc ccacacagac cgcgtttctc 180
tocagtgtog acctacacac toactgetet taccagatga tgttgccaga gtcagtagcc 240
attgtttgct cccccaagtt ccaggaaact ggattcttta aactaactga ccatggacta 300
gaggagattt cttcctgtcg ccagaaagga tttcatccac acagcaagga tccacctctg 360
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cetteettet ggatteacea attgttaaca tttttteet eteagetate ettetaattt 780
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<213> Homo sapiens
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cagcagggcc tcatcacact gggctggatt catactcacc ccacacagac cgcgtttetc 180
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<211> 411
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<210> 22
<211> 896
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 230, 320
<223> n = A, T, C or G
<400> 22
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gaccagetea ateteettgt eceggeettt eeggatttet teeeteaget eetgtteeeg 780
gttcagcage cacgcctcct ccttcctggt gcggccggcc tcccacgcct gcctctccag 840
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<210> 23
<211> 111
<212> DNA
<213> Homo sapiens
<400> 23
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attitcctag tggtttgact ttaaaaaataa ataaggttta attitctccc c
<210> 24
<211> 531
<212> DNA
<213> Homo sapiens
<220>
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<222> 472, 494
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attetectge cacageetee egagtagetg ggattacagg tgeeegeeae cacacecage 180
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aaagtcagtc agtgaagtct ctgctctaac tggccacccg gggccattgg cntctgacac 480
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<210> 25
<211> 471
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 377
<223> n = A, T, C or G
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ggtteteact teagtatget atetegacae ettectaate teeagaegea caaagaaaat 360
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<210> 26
<211> 541
<212> DNA
<213> Homo sapiens
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gtggattttg ctcttttaca acatgtacat ccttactggg ctgtgctgtc acagggatgt 360
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cagtattagc atccacatca gacagcctgg tataaccaga gttggtggtt actgattgta 480
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<210> 27
<211> 461
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> 367
<223> n = A, T, C or G
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<210> 28
<211> 541
<212> DNA
<213> Homo sapiens
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aactagacaa gtgtgttaag agtgataagt aaaatgcacg tggagacaag tgcatcccca 180
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aagtctatcc caacatatcc acatettata ttecacaaat taagetgtag tatgtaccet 360
aagacgctgc taattgactg ccacttcgca actcaggggc ggctgcattt tagtaatggg 420
tcaaatgatt cactttttat gatgetteec aaggtgeett ggettetett cecaactgae 480
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<210> 29
<211> 411
<212> DNA
<213> Homo sapiens
<400> 29
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<210> 30
<211> 511
<212> DNA
<213> Homo sapiens
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  <211> 827
  <212> DNA
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  tcacagtgtc cactcaaggg cagcttggtc ctcttgtcct gcagaggcag gctggtgtga 180
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  <211> 291
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  <211> 491
  <212> DNA
  <213> Homo sapiens
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 cccaracgct gttacgtggc acatgactgt acagtgccac gtaacagcac tgtacttttc 240
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 aaaaatgctg gggtgggcca ggcacagctt cacgcctgta atcccagcac tttgggaggc 480
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 <210> 34
 <211> 521
 <212> DNA
 <213> Homo sapiens
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<221> misc feature
<222> 453, 476, 487
<223> n = A, T, C or G
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tggatggaaa tgaaaattac ccgtgtcttg tggatgcaga cggtgatgtg atttccttcc 180
caccaataac caacagtgag aagacaaagg ttaagaaaac gacttctgat ttgtttttgg 240
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<211> 161
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<213> Homo sapiens
<220>
<221> misc feature
<222> 18
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<211> 341
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<213> Homo sapiens
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ctattattag cagtgaggag cagaagcagc tgatgctgta ctatcacaga agacaagagg 180
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<211> 521
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> 516
\langle 223 \rangle n = A, T, C or G
<400> 37
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gtttgagatt aaatgagata atacatgtaa aattatgtgc ctggcataca gcaagattgt 120
tgttgttgtt gatgatgatg atgatgatga taatatttt ctatccccag tgcacaactg 180
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 ctccattagc tctcatctca ccagcccatc attattgtat gtgctgcctt ctgaagcttg 420
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 <210> 38
 <211> 461
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 <213> Homo sapiens
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 <213> Homo sapiens
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 <213> Homo sapiens
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<212> DNA
<213> Homo sapiens
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<211> 451
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<213> Homo sapiens
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<211> 521
<212> DNA
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<210> 46
<211> 481
<212> DNA
<213> Homo sapiens
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а
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<210> 47
<211> 461
<212> DNA
<213> Homo sapiens
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<222> 128
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<212> DNA
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16

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<211> 511
<212> DNA
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<210> 50
<211> 561
<212> DNA
<213> Homo sapiens
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ggetcaegee tgtggtctaa egetttggga ageeegageg ggeggateae aaggteagga 540
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<210> 51
<211> 451
<212> DNA
<213> Homo sapiens
<400> 51
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<211> 311
<212> DNA
<213> Homo sapiens
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<222> 208
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tettttavag ccatcattta aagemggntt etetecaaca egagtetget sasggggggk 240
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<210> 54
<211> 561
<212> DNA
<213> Homo sapiens
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<213> Homo sapiens
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<210> 56
<211> 591
<212> DNA
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<210> 57
<211> 481
<212> DNA
<213> Homo sapiens
<400> 57
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<213> Homo sapiens
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<211> 191
<212> DNA
<213> Homo sapiens
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<211> 381
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<213> Homo sapiens
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<211> 906
<212> DNA
<213> Homo sapiens
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20

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<213> Homo sapiens
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<213> Homo sapiens
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<222> 288
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<212> DNA
<213> Homo sapiens
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<211> 356
<212> DNA
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25

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<211> 571
<212> DNA
<213> Homo sapiens
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<223> n = A, T, C or G
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<210> 85

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<213> Homo sapiens
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<210> 107
<211> 555
<212> DNA
```

```
<213> Homo sapiens
<400> 107
caggaaccgg agcgcgagca gtagctgggt gggcaccatg gctgggatca ccaccatcga 60
ggcggtgaag cgcaagatcc aggttctgca gcagcaggca gatgatgcag aggagcgagc 120
tgagcgcctc cagcgagaag ttgagggaga aaggcgggcc cgggaacagg ctgaggctga 180
ggtggcctcc ttgaaccgta ggatccagct ggttgaagaa gagctggacc gtgctcagga 240
gcgcctggcc actgccctgc aaaagctgga agaagctgaa aaagctgctg atgagagtga 300
gagaggtatg aaggttattg aaaaccgggc cttaaaagat gaagaaaaga tggaactcca 360
ggaaatccaa ctcaaagaag ctaagcacat tgcagaagag gcagatagga agtatgaaga 420
qqtqqctcqt aaqttqqtqa tcattqaaqq aqacttqqaa cqcacaqaqq aacqaqctqa 480
gctqqcaqaq tcccqttqcc qaqaqatqqa tgaqcaqatt aqactgatgg accagaacct 540
                                                                555
gaagtgtctg agtgc
<210> 108
<211> 541
<212> DNA
<213> Homo sapiens
<400> 108
atctacgtca tcaatcaggc tggagacacc atgttcaatc gagctaagct gctcaatatt 60
ggctttcaag aggccttgaa ggactatgat tacaactgct ttgtgttcag tgatgtqqac 120
ctcattccga tggacgaccg taatgcctac aggtgttttt cgcagccacg gcacatttct 180
gttgcaatgg acaagttcgg gtttagcctg ccatatgttc agtattttgg aggtgtctct 240
qctctcagta aacaacagtt tcttgccatc aatggattcc ctaataatta ttggggttgg 300
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ccaaatgctg tagtagggag gtgtcgaatg atccggcatt caagagacaa gaaaaatgag 420
cccaatecte agaggtttga eeggategea catacaaagg aaacgatgeg ettegatggt 480
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<210> 109
<211> 411
<212> DNA
<213> Homo sapiens
<400> 109
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ggagaacaat aagaactgga gacgttgggt gggtcaggga gtgtggtgga ggctcggaga 180
gatggtaaac aaacctgact gctatgagtt ttcaacccca tagtctaggg ccatgagggc 240
gtcagttctt ggtggctgag ggtccttcca cccagcccac ctgggggagt ggagtgggga 300
qttctqccaq qtaaqcaqat qttqtctccc aaqttcctga cccagatgtc tgqcaqqata 360
acgctgacct gttccctcaa caagggacct gaaagtaatt ttgctcttta c
<210> 110
<211> 451
<212> DNA
<213> Homo sapiens
<400> 110
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tgaacctacg agtacaccga ctacgggcgg actaatcttc aactectaca tacttccccc 120
attattecta quaecaggeg acctgegact cettgaegtt gacaategag tagtacteec 180
gattgaagcc cccattcgta taataattac atcacaagac gtcttgcact catgagctgt 240
ccccacatta ggcttaaaaa cagatgcaat tcccggacgt ctaagccaaa ccactttcac 300
cgctacacga ccqqqqqtat actacgqtca atgctctgaa atctgtggag caaaccacag 360
tttcatgccc atcgtcctag aattaattcc cctaaaaatc tttgaaatag ggcccgtatt 420
```

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taccctatag cacccctct accccctcta g
                                                                  451
<210> 111
<211> 541
<212> DNA
<213> Homo sapiens
<400> 111
gctcttcaca cttttattgt taattctctt cacatggcag atacagagct gtcgtcttga 60
agaccaccac tgaccaggaa atgccacttt tacaaaatca tccccccttt tcatgattgg 120
aacagttttc ctgaccgtct gggagcgttg aagggtgacc agcacatttg cacatgcaaa 180
aaaggagtga ccccaaggcc tcaaccacac ttcccagagc tcaccatggg ctgcaggtga 240
cttgccaggt ttggggttcg tgagctttcc ttgctgctgc ggtggggagg ccctcaagaa 300
ctgagaggcc ggggtatgct tcatgagtgt taacatttac gggacaaaag cgcatcatta 360
ggataaggaa cagccacagc acttcatgct tgtgagggtt agctgtagga gcgggtgaaa 420
ggattccagt ttatgaaaat ttaaagcaaa caacggtttt tagctgggtg ggaaacagga 480
aaactgtgat gtcggccaat gaccaccatt tttctgccca tgtgaaggtc cccatgaaac 540
                                                                  541
<210> 112
<211> 521
<212> DNA
<213> Homo sapiens
<400> 112
caaqcqcttq qcqtttqqac ccaqttcaqt qaqqttcttq qqttttqtqc ctttqqqqat 60
tttggtttga cccaqqggtc agccttagga aggtcttcag gaggaggccg agttcccctt 120
cagtaccacc cctctctccc cactttccct ctcccggcaa catctctggg aatcaacagc 180
atattqacac qttqqaqccq aqcctqaaca tqcccctcqq ccccaqcaca tqqaaaaccc 240
cetteettge ctaaggtgte tgagtttetg getettgagg cattteeaga ettgaaatte 300
tcatcagtcc attgctcttg agtctttgca gagaacctca gatcaggtgc acctgggaga 360
aagactttgt ccccacttac agatctatct cctcccttgg gaagggcagg gaatggggac 420
ggtgtatgga ggggaaggga tctcctgcgc ccttcattgc cacacttggt gggaccatga 480
acatetttag tgtetgaget teteaaatta etgeaatagg a
<210> 113
<211> 568
<212> DNA
<213> Homo sapiens
<400> 113
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agratectte aagaaacagg aaaaaactee taaaacacca aaaggaceta gttetgtaga 120
agacattaaa gcaaaaatgc aagcaagtat agaaaaaggt ggttctcttc ccaaagtgga 180
agccaaattc atcaattatg tgaagaattg cttccggatg actgaccaag aggctattca 240
agatetetgg cagtggagga agtetettta agaaaatagt ttaaacaatt tgttaaaaaa 300
ttttccgtct tatttcattt ctgtaacagt tgatatctgg ctgtcctttt tataatgcag 360
agtgagaact ttccctaccg tgtttgataa atgttgtcca ggttctattg ccaagaatgt 420
gttgtccaaa atgcctgttt agtttttaaa gatggaactc caccctttgc ttggttttaa 480
gtatgtatgg aatgttatga taggacatag tagtagcggt ggtcagacat ggaaatggtg 540
qqsmqacaaa aatatacatq tgaaataa
<210> 114
<211> 483
<212> DNA
<213> Homo sapiens
<400> 114
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tccgaattcc aagcgaatta tggacaaacg attcctttta gaggattact tttttcaatt 60
tcggttttag taatctaggc tttgcctgta aagaatacaa cgatggattt taaatactgt 120
ttgtggaatg tgtttaaagg attgattcta gaacctttgt atatttgata gtatttctaa 180
ctttcatttc tttactgttt gcagttaatg ttcatgttct gctatgcaat cgtttatatg 240
cacgtttctt taattttttt agattttcct ggatgtatag tttaaacaac aaaaagtcta 300
tttaaaactg tagcagtagt ttacagttct agcaaagagg aaagttgtgg ggttaaactt 360
tgtattttct ttcttataga ggcttctaaa aaggtatttt tatatgttct ttttaacaaa 420
tattgtgtac aacctttaaa acatcaatgt ttggatcaaa acaagaccca gcttattttc 480
                                                                  483
tgc
<210> 115
<211> 521
<212> DNA
<213> Homo sapiens
<400> 115
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ggcccccggc agcgccggcc actacgaact gccgtgggtt gaaaaatata ggccagtaaa 120
gctgaatgaa attgtcggga atgaagacac cgtgagcagg ctagaggtct ttgcaaggga 180
aggaaatgtg cccaacatca tcattgcggg ccctccagga accggcaaga ccacaagcat 240
tctgtgcttg gcccqggccc tqctgggccc agcactcaaa gatgccatgt tggaactcaa 300
tgcttcaaat gacaggggca ttgacgttgt gaggaataaa attaaaatgt ttgctcaaca 360
aaaagtcact cttcccaaag gccgacataa gatcatcatt ctggatgaag cagacagcat 420
gaccgacgga gcccagcaag ccttgaggag aaccatggaa atctactcta aaaccactcg 480
ttcgcccttg cttgtaatgc ttcggataag atcatcgagc c
<210> 116
<211> 501
<212> DNA
<213> Homo sapiens
<400> 116
ctttgcaaag cttttatttc atgtctgcgg catggaatcc acctgcacat ggcatcttag 60
ctgtgaagga gaaagcagtg cacgagaagg aatgagtggg cggaaccaac ggcctccaca 120
agetgeette cageageetg ccaaggeeat ggeagagaga gaetgeaaac aaacacaage 180
aaacagagtc tcttcacagc tggagtctga aagctcatag tggcatgtgt gaatctgaca 240
aaattaaaag tgtgcatagt ccattacatg cataaaacac taataataat cctgtttaca 300
cgtgactgca gcaggcaggt ccagctccac cactgccctc ctgccacatc acatcaagtg 360
ccatggttta gagggttttt catatgtaat tcttttattc tgtaaaaggt aacaaaatat 420
acagaacaaa actttccctt tttaaaacta atgttacaaa tctgtattat cacttggata 480
taaatagtat ataagctgat c
<210> 117
<211> 451
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 320
<223> n = A, T, C or G
<400> 117
caagggatat atgttgaggg tacrgrgtga cactgaacag atcacaaagc acgagaaaca 60
ttagttctct ccctcccag cgtctccttc gtctccttg ttttccgatg tccacagagt 120
gagattgtcc ctaagtaact gcatgatcag agtgctgkct ttataagact cttcattcag 180
cgtatccaat tcagcaattg cttcatcaaa tgccgttttt gccaggctac aggccttttc 240
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aggagagttt agaateteat agtaaaagae tgagaaattt agtgecagae caagacgaat 300

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tgggtgtgta ggctgcattn ctttcttact aatttcaaat gcttcctggt aagcctgctg 360
qgaqttcqac acaaqtqqtt tqtttqttqc tccaqatqcc acttcaqaaa qatacctaaa 420
ataatctcct ttcattttca aagtagaaca c
<210> 118
<211> 501
<212> DNA
<213> Homo sapiens
<400> 118
teeggageeg gggtagtege egeegeegee geeggtgeag ceaetgeagg caeeggtgee 60
gccgcctgag tagtgggctt aggaaggaag aggtcatctc gctcggagct tcgctcggaa 120
gggtctttgt tccctgcagc cctcccacgg gaatgacaat ggataaaagt gagctggtac 180
agaaagccaa actcgctgag caggctgagc gatatgatga tatggctgca gccatgaagg 240
cagtcacaga acaggggcat gaactctcca acgaagagag aaatctgctc tctgttgcct 300
acaagaatgt ggtaaggccg cccgccgctc ttcctggcgt gtcatctcca gcattgagca 360
gaaaacagag aggaatgaga agaagcagca gatgggcaaa gagtaccgtg agaagataga 420
ggcagaactg caggacatct gcaatgatgt tctggagctt gttggacaaa tatcttattc 480
caatgctaca caacccagaa a
                                                                  501
<210> 119
<211> 391
<212> DNA
<213> Homo sapiens
<400> 119
aaaaaqcaqc arqttcaaca caaaataqaa atctcaaatq taqqataqaa caaaaccaaq 60
tgtgtqaqqq gqqaaqcaac aqcaaaaqqa aqaaatqaqa tqttqcaaaa aaqatqqaqq 120
agggttcccc tctcctctgg ggactgactc aaacactgat gtggcagtat acaccattcc 180
agagtcaggg gtgttcattc ttttttggga gtaagaaaag gtggggatta agaagacgtt 240
tetggagget tagggaccaa ggetggtete ttteccccet cecaaccece ttgatecett 300
tototgatca ggggaaagga gotogaatga gggaggtaga gttggaaagg gaaaggatto 360
cacttgacag aatgggacag actccttccc a
<210> 120
<211> 421
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 409
<223> n = A, T, C or G
<400> 120
tggcaatagc acagccatcc aggagctctt cargcgcatc tcggagcagt tcactgccat 60
gttccgccgg aaggccttcc tccactggta cacaggcgag ggcatggacg agatggagtt 120
caccgagget gagageaaca tgaacgacet cgtetetgag tateaageag taccaggatg 180
ccaccgcaga agaggaggag gatttcggtg aggaggccga agaggaggcc taaggcagag 240
cocceateac cteaggette teagtteect tageegtett acteaactge ccettteete 300
teceteagaa tttgtgtttg etgeetetat ettgtttttt gtttttett etgggggggt 360
ctagaacagt gcctggcaca tagtaggcgc tcaataaata cttggttgnt gaatgtctcc 420
<210> 121
<211> 206
<212> DNA
<213> Homo sapiens
```

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<400> 121
agetggeget agggeteggt tgtgaaatac agegtrgtea geeettgege teagtgtaga 60
aacccacgcc tgtaaggtcg gtcttcgtcc atctgctttt ttctgaaata cactaagagc 120
agccacaaaa ctgtaacctc aaggaaacca taaagcttgg agtgccttaa tttttaacca 180
gtttccaata aaacggttta ctacct
<210> 122
<211> 131
<212> DNA
<213> Homo sapiens
<400> 122
ggagatgaag atgaggaagc tgagtcagct acgggcargc gggcagctga agatgatgag 60
gatgacgatg tcgataccaa gaagcagaag accgacgagg atgactagac agcaaaaaag 120
gaaaagttaa a
<210> 123
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 166, 202, 222, 225
<223> n = A, T, C or G
<400> 123
gatgaaaatt aaatacttaa attaatcaaa aggcactacg ataccaccta aaacctactg 60
cctcagtggc agtakgctaa kgaagatcaa gctacagsac atyatctaat atgaatgtta 120
gcaattacat akcargaagc atgtttgctt tccagaagac tatggnacaa tggtcattwg 180
ggcccaagag gatatttggc cnggaaagga tcaagataga tnaangtaaa g
<210> 124
<211> 521
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 284, 412, 513
<223> n = A, T, C or G
<400> 124
gagtagcaac gcaaagcgct tggtattgag tctgtgggsg acttcggttc cggtctctgc 60
agcagecgtg ategettagt ggagtgetta gggtagttgg ecaggatgee gaatateaaa 120
atetteagea ggeageteee accaggaett ateteasaaa attgetgaee geetgggeet 180
ggagctaggc aaggtggtga ctaagaaatt cagcaaccag gagacctgtg tggaaattgg 240
tgaaagtgta ccgtggagag gatgtctaca ttgttcagag tggntgtggc gaaatcaatg 300
acaatttaat ggagcttttg atcatgatta atgcctgcaa gattgcttca gccagccggg 360
ttactgcagt catcccatgc ttcccttatg ccccggcagg ataagaaaga tnagagccgg 420
gccgccaatc tcagccaagc ttggtgcaaa tatgctatct gtagcagtgc agatcatatt 480
atcaccatgg acctacatgc ttctcaaatt canggctttt t
                                                                   521
<210> 125
<211> 341
<212> DNA
<213> Homo sapiens
```

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<220>
<221> misc feature
<222> 277
<223> n = A, T, C or G
<400> 125
atgcaaaagg ggacacaggg ggttcaaaaa taaaaatttc tcttccccct ccccaaacct 60
gtaccccagc tccccgacca caaccccctt cctccccgg ggaaagcaag aaggagcagg 120
tgtggcatct gcagctggga agagagaggc cggggaggtg ccgagctcgg tgctggtctc 180
tttccaaata taaatacgtg tgtcagaact ggaaaatcct ccagcaccca ccacccaage 240
acteteegtt ttetgeeggt gtttggagag gggeggnggg eaggggegee aggeaeegge 300
tggctgcggt ctactgcatc cgctgggtgt gcaccccgcg a
<210> 126
<211> 521
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 353, 399, 455
<223> n = A, T, C or G
<400> 126
aggttggaga aggtcatgca ggtgcagatt gtccaggskc agccacaggg tcaagcccaa 60
caggeccaga gtggcactgg acagaccatg caggtgatgc agcagatcat cactaacaca 120
ggagagatec agcagatece ggtgcagetg aatgccggcc agctgcagta tatccgctta 180
gcccagcctg tatcaggcac tcaagttgtg cagggacaga tccagacact tgccaccaat 240
gctcaacaga ttacacagac agaggtccag caaggacagc agcagttcaa gccagttcac 300
aagatggaca gcagctctac cagatccagc aagtcaccat gcctgcgggc cangacctcg 360
ccagcccatg ttcatccagt caagccaacc agcccttcna cgggcaggcc ccccaggtga 420
ccggcgactg aagggcctga gctggcaagg ccaangacac ccaacacaat ttttgccata 480
cagoccccag gcaatgggca cagoctttct toccagagga c
<210> 127
<211> 351
<212> DNA
<213> Homo sapiens
<400> 127
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aatgcattta aaaaataaaa gggaggtggg cagcaaacac acaaagtcct agtttcctgg 120
gtccctggga gaaaagagtg tggcaatgaa tccacccact ctccacaggg aataaatctg 180
tetettaaat geaaagaatg ttteeatgge etetggatge aaatacaeag agetetgggg 240
tcagagcaag ggatggggag aggaccacga gtgaaaaagc agctacacac attcacctaa 300
ttccatctga gggcaagaac aacgtggcaa gtcttggggg tagcagctgt t
<210> 128
<211> 521
<212> DNA
<213>. Homo sapiens
<400> 128
tccagacatg ctcctgtcct aggcggggag caggaaccag acctgctatg ggaagcagaa 60.
agagttaagg gaaggtttcc tttcattcct gttccttctc ttttgctttt gaacagtttt 120
taaatatact aatagctaag tcatttgcca gccaggtccc ggtgaacagt agagaacaag 180
gagettgeta agaattaatt ttgetgtttt teaccecatt caaacagage tgeeetgtte 240
```

. 40

```
cctgatggag ttccattcct gccagggcac ggctgagtaa cacgaagcca ttcaagaaag 300
gegggtgtga aateactgcc accecatgga cagaccectc actetteett ettageegea 360
gcgctactta ataaatatat ttatactttg aaattatgat aaccgatttt tcccatgcgg 420
catectaagg geacttgeea getettatee ggacagteaa geactgttgt tggacaacag 480
                                                                521
ataaaggaaa agaaaaagaa gaaaacaacc gcaacttctg t
<210> 129
<211> 521
<212> DNA
<213> Homo sapiens
<400> 129
tgagacggac cactggcctg gtccccctc atktgctgtc gtaggacctg acatgaaacg 60
cagatctagt ggcagagagg aagatgatga ggaacttctg agacgtcggc agcttcaaga 120
agagcaatta atgaagctta actcaggcct gggacagttg atcttgaaag aagagatgga 180
gaaagagagc cgggaaaggt catctctgtt agccagtcgc tacgattctc ccatcaactc 240
agetteacat attecateat etaaaaetge ateteteeet ggetatggaa gaaatggget 300
tcaccqqcct gtttctaccq acttcqctca qtataacaqc tatqqqqatq tcaqcqqqqq 360
agtgcgagat taccagacac ttccagatgg ccacatgcct gcaatgagaa tggaccgagg 420
agtgtctatg cccaacatgt tggaaccaaa gatatttcca tatgaaatgc tcatggtgac 480
caacagaggg ccgaaaccaa atctcagaga ggtggacaga a
                                                                   521
<210> 130
<211> 270
<212> DNA
<213> Homo sapiens
<400> 130
tcactttatt tttcttgtat aaaaacccta tgttgtagcc acagctggag cctgagtccg 60
ctgcacggag actctggtgt gggtcttgac gaggtggtca gtgaactcct gatagggaga 120
cttggtgaat acagtctcct tccagaggtc gggggtcagg tagctgtagg tcttagaaat 180
ggcatcaaag gtggccttgg cgaagttgcc cagggtggca gtgcagcccc gggctgaggt 240
gtagcagtca tcgataccag ccatcatgag
<210> 131
<211> 341
<212> DNA
<213> Homo sapiens
<400> 131
ctggaatata gacccgtgat cgacaaaact ttgaacgagg ctgactgtgc caccgtcccg 60
ccagccattc gctcctactg atgagacaag atgtggtgat gacagaatca gcttttgtaa 120
ttatgtataa tageteatge atgtgteeat gteataactg tetteataeg ettetgeaet 180
ctggggaaga aggagtacat tgaagggaga ttggcaccta gtggctggga gcttgccagg 240
aacccagtgg ccagggagcg tggcacttac ctttgtccct tgcttcattc ttgtgagatg 300
ataaaactgg gcacagctct taaataaaat ataaatgaac a
                                                                   341
<210> 132
<211> 844
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 37
<223> n = A, T, C or G
<400> 132
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41

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agggcaagaa cgtgatcggg ttacagatgg gcaccaaccg cggggcgtct cangcaggca 180
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ccccagagct ctcaagctcc tttctgtcag ggtggggggt tcaagcctgt cctgtcacct 360
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<210> 156
<211> 670
<212> DNA
<213> Homo sapiens
<400> 156
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acacaggtgg tgggacagac aggtgtcatc cqcagtgtca cggggggcat gtgctctgtg 180
tacctgaagg acagtgagaa ggttgtcagc atttccagtg agcacctgga gcctatcacc 240
cccaccaaga acaacaaggt gaaagtgatc ctgggcgagg atcgggaagc cacgggcgtc 300
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cctcctgcag ggctaggcgg attgttctgg atttcctttt gtttttcctt ttaggtttcc 540
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<210> 157
<211> 421
<212> DNA
<213> Homo sapiens
<400> 157
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aagaatcgag ttgaaatcaa tgatgtggag cctgaagttt ttaaggaaat gatgtgcttc 180
atttacacgg ggaaggctcc aaacctcgac aaaatggctg atgatttgct ggcagctgct 240
gacaagtatg ccctggagcg cttaaaggtc atgtgtgagg atgccctctg cagtaacctg 300
teegtggaga acgetgeaga aatteteate etggeegace teeacagtge agateagttg 360
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<210> 158
<211> 321
<212> DNA
<213> Homo sapiens
<400> 158
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gttccatgcc aattggtgaa atagaacctc atccggtagt ggagccggag ggacatcttg 120
tcatcaacgg tgatggtgcg atttggagca taccagagct tggtgttctc gccatacagg 180
gcaaagaggt tgtgacaaag aggagagata cggcatgcct gtgcagccct gatgcacagt 240
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atcacttcca cccctggctt g
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49

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<210> 159
<211> 596
<212> DNA
<213> Homo sapiens
<400> 159
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gggaattcat tttcatcact gggagtgtcc ttagtgtata aaaaccatgc tggtatatgg 180
cttcaagttg taaaaatgaa agtgacttta aaagaaaata ggggatggtc caggatctcc 240
actgataaga ctgtttttaa gtaacttaag gacctttggg tctacaagta tatgtgaaaa 300
aaatgagact tactgggtga ggaaattcat tgtttaaaga tggtcgtgtg tgtgtgtgtg 360
ttgaaattac tgkgtaaata tatgtytgat aatgatttgc tytttgvcma ctaaaattag 480
gvctgtataa gtwctaratg cmtccctggg kgttgatytt ccmagatatt gatgatamcc 540
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<211> 515
<212> DNA
<213> Homo sapiens
<400> 160
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taaggggcgc ctgccagggc cacggccagg aggca
<210> 161
<211> 936
<212> DNA
<213> Homo sapiens
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accaegeeca egtecaeete gteeteeeet geegeeaegt eetgggegge caaggtetee 240
aaaattgate teeagetgag acgttatate atttgetgge tteeggaaat gatggteeat 300
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ctettcaact tcatteteet tattttcagt gtetgecact ggatgatgtt etteacette 540
aggtgtttcc tcaqtcacat ttgattgatc caagtcagtt aattcqtctt tqacaqttcc 600
ccagttgtga gatccgctac ctccacgttt gtcctcgtgc ttcaggccag atctatcact 660
tecaetatge etateaaatt caegtttgee aegagaatea aateeatete eteggeeeat 720
tecacgteca eggeeeete gaeetettee aagaeeacea egaeetegaa taggteggte 780
aataatcggt ctatcaactg aaaattcgcc tccttcaccc ttttcttcaa gtggcttttc 840
gaatcttegt teaegaggtg gtegeettte tggtetteta teaattattt teeetteaec 900
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<210> 162

50

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<211> 950
<212> DNA
<213> Homo sapiens
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gcgaagatga agtttggctg cctctccttc cggcagcctt atgctggctt tgtcttaaat 180
ggaatcaaga ctgtggagac gcgctggcgt cctctgctga gcagccagcg gaactgtacc 240
ategeegtee acattgetea cagggactgg gaaggegatg cetgteggga getgetggtg 300
gagagactcg ggatgactcc tgctcagatt caggccttgc tcaggaaagg ggaaaagttt 360
qqtcqaqqaq tqataqcqqq actcqttqac attqqqqaaa ctttqcaatq cccqaaqac 420
ttaactcccg atgaggttgt ggaactagaa aatcaagctg cactgaccaa cctgaagcag 480
aagtacctga ctgtgatttc aaaccccagg tggttactgg agcccatacc taggaaagga 540
ggcaaggatg tattccaggt agacatccca gagcacctga tccctttggg gcatgaagtg 600
tgacaagtgt gggctcctga aaggaatgtt ccrgagaaac cagctaaatc atggcacctt 660
caatttgcca tcgtgacgca gacctgtata aattaggtta aagatgaatt tccactgctt 720
tggagagtec cacceactaa geactgtgea tgtaaacagg tteetttget cagatgaagg 780
aagtaggggg tggggctttc cttgtgtgat gcctccttag gcacacaggc aatgtctcaa 840
qtactttgac cttagggtag aaggcaaagc tgccagtaaa tgtctcagca ttgctgctaa 900
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<210> 163
<211> 475
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 301, 317, 331, 458, 464, 470
<223> n = A, T, C or G
<400> 163
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ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtgt 180
acacctgtgg ttctcggggc tgccctttgg ctttggagat ggttttctcg atgggggctg 240
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ngacggtgag gacgctnacc acacggtacg ngctggtgta ctgctcctcc cgcggctttg 360
tettggcatt atgeacetee acgeegteea egtaceaatt gaacttgace teagggtett 420
cgtggctcac gtccaccacc acgcatgtaa cctcaaanct cggncgcgan cacgc
<210> 164
<211> 476
<212> DNA
<213> Homo sapiens
<400> 164
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gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca 180
ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc 240
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cctgcccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct gcctggtcaa 360
aggettetat eccagegaca tegecegtgg agtgggagag caatgggeag eeggagaaca 420
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<210> 165

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<211> 256
  <212> DNA
  <213> Homo sapiens
  <220>
  <221> misc_feature
  \langle 222 \rangle 10, \overline{37}, 249
  <223> n = A, T, C or G
  <400> 165
  agcgtggttn cggccgaggt cccaaccaag gctgcancct ggatgccatc aaagtcttct 60
  gcaacatgga gactggtgag acctgcgtgt accccactca gcccagtgtg gcccagaaga 120
  actggtacat cagcaagaac cccaaggaca agaggcatgt ctggttcggc gagagcatga 180
  ccgatggatt ccagttcgag tatggcggcc agggctccga ccctgccgat gtggacctgc 240
  ccgggcggnc gctcga
  <210> 166
. <211> 332
  <212> DNA
  <213> Homo sapiens
  <400> 166
  agcgtggtcg cggccgaggt caagaacccc gcccgcacct gccgtgacct caagatgtgc 60
  cactctgact ggaagagtgg agagtactgg attgacccca accaaggctg caacctggat 120
  gccatcaaag tcttctgcaa catggagact ggtgagacct gcgtgtaccc cactcagccc 180
  agtgtggccc agaagaactg gtacatcagc aagaacccca aggacaagag gcatgtctgg 240
  ttcggcgaga gcatgaccga tggattccag ttcgagtatg gcggccaggg ctccgaccct 300
  gccgatgtgg acctgcccgg gcggccgctc ga
                                                                      332
  <210> 167
  <211> 332
  <212> DNA
  <213> Homo sapiens
  <220>
  <221> misc feature
  <222> 77, 109, 136, 184, 198
  <223> n = A, T, C or G
  <400> 167
  tegageggte geeegggeag gtecacateg geagggtegg agecetggee geeatacteg 60
  aactggaatc catcggncat getctcgccg aaccagacat gectcttgnc cttggggttc 120
  ttgctgatgt accagntctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
  ccantctcca tgttgcanaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
  atccagtact ctccactctt ccagacagag tggcacatct tgaggtcacg gcaggtgcgg 300
  gcggggttct tgacctcggt cgcgaccacg ct
                                                                      332
  <210> 168
  <211> 276
  <212> DNA
  <213> Homo sapiens
  <220>
  <221> misc feature
  <222> 72, 84
  <223> n = A, T, C or G
  <400> 168
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gatgcacggc aaggcccagt gactgcgttg gcggtgcagt attcttcata gttgaacata 180
tegetggagt ggaetteaga atectgeett etgggageae ttgggaeaga ggaateeget 240
gcattectgc tggtggacct cggccgcgac cacgct
<210> 169
<211> 276
<212> DNA
<213> Homo sapiens
<400> 169
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caccgccaac geagteactg ggeettgeeg tgeateette ceaegetggt actttgaegt 180
ggagaggaac teetgeaata aetteateta tggaggetge eggggeaata agaacageta 240
ccgctctgag gaggacctgc ccgggcggcc gctcga
<210> 170
<211> 332
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 294
<223> n = A, T, C or G
<400> 170
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ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact etccactett ecagecagaa tggcacatet tgaggteacg gcangtgegg 300
gcggggttct tgacctcggc cgcgaccacg ct
<210> 171
<211> 333
<212> DNA
<213> Homo sapiens
<400> 171
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tgccatcaaa gtcttctgca acatggagac tggtgagacc tgcgtgtacc ccactcagcc 180
cagtgtggcc cagaagaact ggtacatcag caagaacccc aaggacaaga ggcatgtctg 240
gctcggcgag agcatgaccg atggattcca gttcgagtat ggcggccagg gctccgaccc 300
tgccgatgtg gacctgcccg ggcggccgct cga
<210> 172
<211> 527
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 46, \overline{1}25, 140, 148, 220, 229, 291, 388, 456
<223> n = A, T, C or G
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<400> 172

<210> 175

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cctgnaatgg ggcccatgan atggttgnct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtet tggcctatgc cttatggggg tggccgttgn gggcggtgng gtccgcctaa 240
aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca naagtgccag 300
gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctgntc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgctgtct ttttccttcc aatcangggc tcgctcttct gaatattctt 480
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                                                                  527
<210> 173
<211> 635
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 444, 453, 517, 540, 546, 551, 573, 593
<223> n = A, T, C or G
<400> 173
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gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agacceettt egteacceae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatett tgangaacat ggntttagge ggaccacace ggecacaacg 480
ggcaccccca taaggcatag gccaagaaca tacccgncga atgtaggaca agaagctctn 540
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catcctggtg gcactgataa aaacccttac agtta
<210> 174
<211> 572
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 457, 511, 520, 552, 568
<223> n = A, T, C or G
<400> 174
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actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcgqcg 180
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gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttqaa 360
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gttggggaag ctcgtctgtc tttttccttc caatcanggg ctcgctcttc tgattattct 480
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ctgtgacacc anggcggggc cgaagganca ct
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<213> Homo sapiens

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<211> 372
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 247
<223> n = A, T, C or G
<400> 175
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aacgaagget tgaaccaacc tacggatgac tegtgetttg accectacac agttteccat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttangct ttggaagtgg tcatttcaga tgtgattcat ctagatggtg ccatgacaat 300
ggtgtgaact acaagattgg agagaagtgg gaccgtcagg gagaaaatgg acctgcccgg 360
gcggccgctc ga
<210> 176
<211> 372
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 251
<223> n = A, T, C or G
<400> 176
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aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ntgacagagt tgeccaeggt aacaacetet teeegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggta cctctggtga ggacctcggc 360
cgcgaccacg ct
<210> 177
<211> 269
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 94, 225
<223> n = A, T, C or G
<400> 177
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tetcageett ggttetecag etaatggtga tggnggtete agtageatet gteacacgag 120
cccttcttgg tgggctgaca ttctccagag tggtgacaac accctgagct ggtctgcttg 180
tcaaagtgtc cttaagagca tagacactca cttcatattt ggcgnccacc ataagtcctg 240
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<210> 178
<211> 529
<212> DNA
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<400> 178
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caccaactga cctgaagttc actcaggtca cacccacaag cctgagcgcc cagtggacac 180
cacccaatgt teageteact ggatategag tgegggtgac ceccaaggag aagaceggac 240
caatgaaaga aatcaacctt gctcctgaca gctcatccgt ggttgtatca ggacttatgg 300
cggccaccaa atatgaagtg agtgtctatg ctcttaagga cactttgaca agcagaccag 360
ctcagggtgt tgtcaccact ctggagaatg tcagcccacc aagaagggct cgtgtgacag 420
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<210> 179
<211> 454
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 64
<223> n = A, T, C or G
<400> 179
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tagntcttct cgaagtcccg ggccagcagc tccacggggt ggtctcctgc ctccaggcgc 120
ttctcattct catggatctt cttcacccgc agcttctgct tctcagtcag aaggttgttg 180
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ggqaattcqq tcaqctcaqa qtccaqqcaa qqqqqqatqt atttqcaaqq cccqatqtaq 300
tocaagtgga gottgtggco ottottggtg cootocaagg tgcactttgt ggcaaagaag 360
tggcaggaag agtcgaaggt cttgttgtca ttgctgcaca ccttctcaaa ctcgccaatg 420
ggggctgggc agacctgccc gggcggccgc tcga
<210> 180
<211> 454
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 55, 299, 317, 332, 342, 348
<223> n = A, T, C or G
<400> 180
tegageggee geeegggeag gtetgeeeag eecceattgg egagtttgag aaggngtgea 60
gcaatgacaa caagacette gactetteet gccacttett tgccacaaag tgcaccetgg 120
agggcaccaa gaagggccac aagctccacc tggactacat cgggccttgc aaatacatcc 180
cccttgcct ggactctgag ctgaccgaat tccccttgcg catgcgggac tggctcaaga 240
acqtcctggt caccctgtat qaqaqqqatg aqqacaacaa ccttctgact qaqaaqcana 300
agctgcgggt gaagaanatc catgagaatg anaagcgcct gnaggcanga gaccaccccq 360
tggagctgct ggcccgggac ttcgagaaga actataacat gtacatcttc cctgtacact 420
ggcagttcgg ccagacctcg gccgcgacca cgct
                                                                   454
<210> 181
<211> 102
<212> DNA
<213> Homo sapiens
<220>
```

```
<221> misc feature
\langle 222 \rangle 8, 47, 60, 67
<223> n = A, T, C or G
<400> 181
agcgtggntg cggacgacgc ccacaaagcc attgtatgta gttttanttc agctgcaaan 60
aataccncca gcatccacct tactaaccag catatgcaga ca
<210> 182
<211> 337
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 169, 195, 253, 314
<223> n = A, T, C or G
<400> 182
tcgagcggtc gcccgggcag gtctgggcgg atagcaccgg gcatattttg gaatggatqa 60
ggtctggcac cctgagcagc ccagcgagga cttggtctta gttgagcaat ttggctagga 120
ggatagtatg cagcacggtt ctgagtctgt gggatagctg ccatgaagna acctgaagga 180
ggcgctggct ggtangggtt gattacaggg ctgggaacag ctcgtacact tgccattctc 240
tgcatatact ggntagtgag gcgagcctgg cgctcttctt tgcgctgagc taaagctaca 300
tacaatggct ttgnggacct cggccgcgac cacgctt
<210> 183
<211> 374
<212> DNA
<213> Homo sapiens
<400> 183
tegageggee geeegggeag gteeatttte teeetgaegg teceaettet eteeaatett 60
gtagttcaca ccattgtcat gacaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tecaaeggea taatgggaaa etgtgtaggg qteaaageae gagteateeg taggttggtt 240
caageetteg ttgacagaag ttgcccaegg taacaacete ttecegaace ttatgeetet 300
getggtettt caagtgeete eactatgatg ttgtaggtgg caeetetggt gaggaeeteg 360
gccgcgacca cgct
<210> 184
<211> 375
<212> DNA ·
<213> Homo sapiens
<220>
<221> misc_feature
<222> 30, 174, 248, 285, 306, 332, 345, 368
<223> n = A, T, C or G
<400> 184
agegtggttt geggeegagg teeteacean aggtgeeace tacaacatea tagtggagge 60
actgaaagac cagcagaggc ataaggttcg ggaagaggtt gttaccgtgg gcaactctgt 120
caacgaaggc ttgaaccaac ctacggatga ctcgtgcttt gacccctaca cagnttccca 180
ttatgccgtt ggagatgagt gggaacgaat gtctgaatca ggctttaaac tgttgtgcca 240
gtgcttangc tttggaagtg gtcatttcag atgtgattca tctanatggt gtcatgacaa 300
tggtgngaac tacaagattg gagagaagtg gnaccgtcag ggganaaaat ggacctgccc 360
gggcggcncg ctcga
                                                                   375
```

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<210> 185
<211> 148
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 28, 36, 86
<223> n = A, T, C or G
<400> 185
agcgtggtcg cggccgaggt ctggcttnct gctcangtga ttatcctgaa ccatccaggc 60
caaataagcg ccggctatgc ccctgnattg gattgccaca cggctcacat tgcatgcaag 120
tttgctgagc tgaaggaaaa gattgatc
<210> 186
<211> 397
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 78
<223> n = A, T, C or G
<400> 186
togagogoo goooggoog gtocaattga aacaaacagt totgagacog ttottocaco 60
actgattaag agtggggngg cgggtattag ggataatatt catttagcct tctgagcttt 120
ctgggcagac ttggtgacct tgccagctcc agcagccttc tggtccactg ctttgatgac 180
acceacegea actgtetgte teatateaeg aacageaaag egacecaaag gtggatagte 240
tgagaagete teaacacaca tgggettgee aggaaceata teaacaatgg geageateae 300
cagacttcaa gaatttaagg gccatcttcc agctttttac cagaacggcg atcaatcttt 360
tccttcagct cagcaaactt gcatgcaatg tgagccg
<210> 187
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 145, 286, 363, 365, 425, 433, 452, 462, 471, 512, 514, 534,
536, 540, 565, 583
<223> n = A, T, C or G
<400> 187
tcgagcggcc gcccgggcag gtccagaggg ctgtgctgaa gtttgctgct gccactggag 60
ccactccaat tgctggccgc ttcactcctg qaaccttcac taaccagatc caggcagect 120
tccgggagcc acggcttctt gtggntactg accccagggc tgaccaccag cctctcacgg 180
aggeatetta tgttaaceta cetaceattg egetgtgtaa cacagattet cetetgeget 240
atgtggacat tgccatccca tgcaacaaca agggagctca ctcagngggg tttgatgtgg 300
tggatgctgg ctcgggaagt tctgcgcatg cgtggcacca tttcccgtga acacccatgg 360
gangneatge etgatetgga ettetacaga gateetgaag agattgaaaa agaagaacag 420
gctgnttgct ganaaagcaa gtgaccaagg angaaatttc angggtgaaa nggactgctc 480
ccgctcctga attcactgct actcaacctg angntgcaga ctggtcttga aggngnacan 540
gggccctctg ggcctattta agcancttcg gtcgcgaaca cgnt
```

```
<210> 188
<211> 579
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 7, 1\overline{3}6, 486
<223> n = A, T, C or G
<400> 188
agcgtgngtc gcggccgagg tgctgaatag gcacagaggg cacctgtaca ccttcagacc 60
agtctgcaac ctcaggctga gtagcagtga actcaggagc gggagcagtc cattcaccct 120
gaaatteete ettggneaet geetteteag eageageetg etettettt teaatetett 180
caggatetet gtagaagtac agateaggea tgaceteeca tgggtgttea egggaaatgg 240
tgccacgcat gcgcagaact tcccgagcca gcatccacca catcaaaccc actgagtgag 300
ctcccttgtt gttgcatggg atgggcaatg tccacatagc gcagaggaga atctgtgtta 360
cacagogoaa tggtaggtag gttaacataa gatgcctccg cgagaagctg gtggtcagcc 420
ctggggtcaa gtaaccacaa gaagccgtgg ctcccggaag gctgcctgga tctggttagt 480
gaaggntcca ggagtgaagc ggccaacaat tggagtggct tcagtggcaa gcagcaaact 540
tcagcacaag ccctctggac ctgcccggcg gccgctcga
                                                                   579
<210> 189
<211> 374
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 41, 280, 314, 330, 350, 353
<223> n = A, T, C or G
<400> 189
tegageggee geoegggeag gteeatttte teeetgaegg neceaettet etceaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgeccaeggt aacaaceten teeeegaace ttatgeetet 300
gctgggcttt cagngcctcc actatgatgn tgtaggggg cacctctggn gangacctcg 360
geegegaeca eget
<210> 190
<211> 373
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 247, 304, 306, 332, 337
<223> n = A, T, C or G
<400> 190
agcgtggtcg cggccgaggt cctcaccaga ggtgccacct acaacatcat agtggaggca 60
ctgaaagacc agcagaggca taaggctcgg gaagaggttg ttaccgtggg caactctgtc 120
aacgaaggct tgaaccaacc tacggatgac tcgtgctttg acccctacac agtttcccat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttangct ttggaagtgg gtcatttcag atgtgattca tctagatggt gccatgacaa 300
tggngngaac tacaagattg gagagaagtg gnaccgncag ggagaaaatg gacctgcccg 360
```

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ggcggccgct cga
                                                                   373
<210> 191
<211> 354
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 218, 299, 306, 326, 333, 337, 341
<223> n = A, T, C or G
<400> 191
agcgtggtcg cggccgaggt ccacatcggc agggtcggag ccctggccgc catactcgaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
getgatgtac cagttettet gggccacact gggctgagtg gggtacacge aggteteace 180
agtctccatg ttgcagaaga ctttgatggc atccaggntg caaccttggt tggggtcaat 240
ccagtactct ccactcttcc agccagagtg gcacatcttg aggtcacggc aggtgcggnc 300
gggggntttt gcggctgccc tctqqncttc gqntqtnctc natctqctqq ctca
<210> 192
<211> 587
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 276
<223> n = A, T, C or G
<400> 192
tcgagcggcc gcccgggcag gtctcgcggt cgcactggtg atgctggtcc tgttggtccc 60
ceeggeeete etggacetee tggeeeecet ggteeteea gegetggttt egactteage 120
ttcctgcccc agccacctca agagaaggct cacgatggtg gccgctacta ccggggctgat 180
gatgccaatg tggttcgtga ccgtgacctc gaggtggaca ccaccctcaa gagcctgagc 240
cagcagateg agaacateeg gageecagag ggeagnegea agaaceeege eegeacetge 300
cgtgacctca agatgtgcca ctctgactgg aagagtggag agtactggat tgaccccaac 360
caagetgcaa cetggatgce atcaaagtet tetgcaacat ggagaetggt gagaeetgeg 420
tgtaccccac tcagcccagt gtggcccaaa agaactggta catcagcaag aaccccaagg 480
acaagaagca tgtctggttc ggcgagaaca tgaccgatgg attccagttc gagtatggcg 540
ggcagggctc cgaccctgcc gatggggacc ttggccgcga acacgct
<210> 193
<211> 98
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9, 33, 58, 71, 90
<223> n = A, T, C or G
<400> 193
agcgtggnng cggccgaggt ataaatatcc agnccatatc ctccctccac acgctganag 60
atgaagctgt ncaaagatct cagggtggan aaaaccat
<210> 194
<211> 240
```

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<212> DNA
<213> Homo sapiens
<400> 194
tcgagcggcc gcccgggcag gtccttcaga cttggactgt gtcacactgc caggcttcca 60
gggctccaac ttgcagacgg cctgttgtgg gacagtctct gtaatcgcga aagcaaccat 120
ggaagacctg ggggaaaaca ccatggtttt atccaccctg agatctttga acaacttcat 180
ctctcagcgt gcggagggag gctctggact ggatatttct acctcggccg cgaccacgct 240
<210> 195
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 22, 37, 39, 105, 268, 276, 302, 323, 331, 335, 347, 351,
<223> n = A, T, C or G
<400> 195
cgagcgggcg accgggcagg tncagactcc aatccanana accatcaagc cagatgtcag 60
aagctacacc atcacaggtt tacaaccagg cactgactac aaganctacc tgcacacctt 120
gaatgacaat gctcggagct cccctgtggt catcgacgcc tccactgcca ttgatgcacc 180
atccaacctg cgtttcctgg ccaccacacc caattccttg ctggtatcat ggcagccgcc 240
acgtgccagg attaccggta catcatenag tatganaagc ctgggcctcc tcccagagaa 300
quagteecte ggeecegee tgntgteeca naggntacta ttactgngee ngcaacegge 360
aaccqatatc nattttqnca ttqqccttca acaataatta
<210> 196
<211> 494
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 19, \overline{8}3, 168, 252, 271, 292, 430
<223> n = A, T, C or G
<400> 196
agcgtggttc gcggccgang tcctgtcaga gtggcactgg tagaagttcc aggaaccctg 60
aactgtaagg gttcttcatc agngccaaca ggatgacatg aaatgatgta ctcagaagtg 120
tectggaatg gggeeeatga gatggttgte tgagagagag ettettgnee tgtettttte 180
cttccaatca ggggctcgct cttctgatta ttcttcaggg caatgacata aattgtatat 240
tegggteeeg gnteeaggee agtaatagta neetetgtga caecagggeg gngeegaggg 300
accacttctc tgggaggaga cccaggcttc tcatacttga tgatgtaacc ggtaatcctg 360
gcacgtggcg gctgccatga taccagcaag gaattggggt gtggtggcca ggaaacgcag 420
gttggatggn gcatcaatgg cagtggaggc cgtcgatgac cacaggggga gctccgacat 480
tgtcattcaa ggtg
                                                                    494
<210> 197
<211> 118
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
```

```
<222> 8, 71, 96
<223> n = A, T, C or G
<400> 197
agcgtggncg cggccgaggt gcagcgcggg ctgtgccacc ttctgctctc tgcccaacga 60
taaggagggt ncctgcccc aggagaacat taactntccc caqctcggcc tctgccgg
<210> 198
<211> 403
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 41, \overline{5}3, 98, 195, 350
<223> n = A, T, C or G
<400> 198
tegageggee geeegggeag gttttttttg etgaaagtgg ntaetttatt ggntgggaaa 60
gggagaagct gtggtcagcc caagagggaa tacagagncc cgaaaaaggg gagggcaggt 120
gggctggaac cagacgcagg gccaggcaga aactttctct cctcactgct cagcctggtg 180
gtggctggag ctcanaaatt gggagtgaca caggacacct tcccacagcc attgcggcgg 240
catttcatct ggccaggaca ctggctgtcc acctggcact ggtcccgaca gaagcccgag 300
ctggggaaag ttaatgttca cctgggggca ggaaccctcc ttatcattgn gcagagagca 360
gaaggtggca cagcccgcgc tgcacctcgg ccgcgaccac gct
                                                                    403
<210> 199
<211> 167
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 92, 107
<223> n = A, T, C or G
<400> 199
tegageggee geeegggeag gtecaceata agteetgata caaceaegga tgagetgtea 60
ggagcaaggt tgatttettt cattggteeg gnetteteet tgggggneae cegeaetega 120
tatccagtga gctgaacatt gggtggcgtc cactgggcgc tcaggct
<210> 200
<211> 252
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 210, 226, 227, 230, 236
<223> n = A, T, C or G
<400> 200
tegageggtt egeeegggea ggtecaceae acceaattee ttgetggtat catggeagee 60
gccacgtgcc aggattaccg gctacatcat caagtatgag aagcctgggt ctcctcccag 120
agaagcggtc cctcggcccc gccctggtgt cacagaggct actattactg gcctggaacc 180
gggaaccgaa tatacaattt atgtcattgn cctgaagaat aatcannaan agcgancccc 240
tgattggaag ga
```

```
<210> 201
<211> 91
<212> DNA
<213> Homo sapiens
<400> 201
ttttttttt tttttttt tttttt t
<210> 202
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 9, 354
<223> n = A, T, C or G
<400> 202
tegageggne geceggeag gtetgecaac accaagattg geceegeeg catecacaca 60
qtccqtqtqc qqqqaqqtaa caaqaaatac cqtqccctqa qqttqqacqt qqqqaatttc 120
tcctggggct cagagtgttg tactcgtaaa acaaggatca tcgatgttgt ctacaatgca 180
totaataacg agctggttcg taccaagacc ctggtgaaga attgcatcgt gctcatcgac 240
agcacaccgt accgacagtg gtacgagtcc cactatgcgc tgcccctggg ccgcaagaag 300
ggagccaagc tgactcctga ggaagaagag attttaaaca aaaaacgatc taanaaaaaa 360
aaaacaat
<210> 203
<211> 340
<212> DNA
<213> Homo sapiens
<400> 203
agegtggteg eggeegaggt gaaatggtat teagetteet ggeaettetg gteageaace 60
cagtgttggg caacaaatga tctttgagga acatggtttt aggcggacca caccgcccac 120
aacggccacc cccataaggc ataggccaag accatacccg ccgaatgtag gacaagaagc 180
teteteteag acaaccatet catgggeece attecaggae acttetgagt acateattte 240
atgtcatcct gttggcactg atgaagaacc cttacagttc agggttcctg gaacttctac 300
cagtgccact ctgacaggac ctgcccgggc ggccgctcga
<210> 204
<211> 341
<212> DNA
<213> Homo sapiens
<400> 204
tcgagcggcc gcccgggcag gtcctgtcag agtggcactg gtagaagttc caggaaccct 60
gaactgtaag ggttcttcat cagtgccaac aggatgacat gaaatgatgt actcagaagt 120
gtcctggaat ggggcccatg agatggttgt ctgagagaga gcttcttgtc ctacattcgg 180
egggtatggt cttggcctat gccttatggg ggtggccgtt gtgggcggtg tggtccgcct 240
aaaaccatgt teetcaaaga teatttgttg eecaacactg ggttgetgae cagaagtgee 300
aggaagetga ataccattte aceteggeeg egaceaeget a
                                                                341
<210> 205
<211> 770
<212> DNA
<213> Homo sapiens
```

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<220>
<221> misc feature
<222> 529, 591, 623, 626, 629, 630, 656, 702, 709, 712, 717, 743,
746, 749, 759, 762, 766
<223> n = A, T, C or G
<400> 205
tegageggee geeegggeag gteteeette ttgeggeeca ggggeagege atagtgggae 60
tegtaceact gteggtacgg tgtgetgteg atgageacga tgeaattett caccagggte 120
ttggtacgaa ccagctcgtt attagatgca ttgtagacaa catcgatgat ccttgtttta 180
cgagtacaac actctgagcc ccaggagaaa ttccccacgt ccaacctcag ggcacggtat 240
ttettgttac eteceegeac acggactgtg tggatgegge gggggecaag etgacteetg 300
aggaagaaga gattttaaac aaaaaacgat ctaaaaaaat tcagaagaaa tatgatgaaa 360
ggaaaaagaa tgccaaaatc agcagtctcc tggaggagca gttccagcag ggcaagcttc 420
ttgcgtgcat cgcttcaagg ccgggacagt gtgaccgagc agatggctat gtgctagagg 480
gcaaagaagt ggagttctat cttaagaaaa tcagggccca gaatggtgng tcttcaacta 540
atccaaaggg gagtttcaga ccagtgcaat cagcaaaaac attgatactg ntggccaaat 600
ttattqqtqc aggqcttqca cantangann qqctqqqtct tqqqqcttqq attqqnacaa 660
gctttggcag ccttttcttt ggttttgcca aaaacctttt gntgaagang anacctnggg 720
cggacccett aaccgattcc acncenggng gcgttctang gnccencttq
<210> 206
<211> 810
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 574, 621, 625, 636, 668, 673, 704, 728, 743, 767, 772, 786,
789, 807, 809, 810
<223> n = A, T, C or G
<400> 206
agcgtggtcg cggccgaggt ctgctgcttc agcgaagggt ttctggcata accaatgata 60
aggetgecaa agaetgttee aataceagea eeagaaceag eeacteetae tgttgeagea 120
cctgcaccaa taaatttggc agcagtatca atgtctctgc tgattgcact ggtctgaaac 180
tecetttgga ttagetgaga cacaccatte tgggeeetga tttteetaag atagaactee 240
aactetttge cetetageae atagecatet geteggteae aetgteeegg cettgaageg 300
atgcacgcaa gaagcttgcc ctgctggaac tgctcctcca ggagactgct gattttggca 360
ttctttttcc tttcatcata tttcttctga atttttttag atcgtttttt gtttaaaatc 420
tettetteet caggagteag ettggeecee geegeateea caeagteegt gtgeggggag 480
gtaacaagaa ataccgtgcc ctgaggttgg acgtggggaa tttctcctgg ggctcagagt 540
ggtgtactcg taaaacaagg atcatcgatg gtgnctacaa tgcatctaat aacgagctgg 600
gtcggaccca aagaacctgg ngaanaaatg gatcgnctca tcgacaggac accgtacccg 660
acaggggnac ganteceact atgegettge eeetgggeeg caanaaagga aaactgeeeg 720
ggcggccntc gaaagcccaa ttntggaaaa aatccatcac actgggnggc cngtcgagca 780
tgcatntana ggggcccatt ccccctnann
                                                                  810
<210> 207
<211> 257
<212> DNA
<213> Homo sapiens
<400> 207
tcgagcggcc gcccgggcag gtccccaacc aaggctgcaa cctggatgcc atcaaagtct 60
tctgcaacat ggagactggt gagacctgcg tgtaccccac tcagcccagt gtggcccaga 120
agaactggta catcagcaag aaccccaagg acaagaggca tgtctggttc ggcgagagca 180
```

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tgaccgatgg attccagttc gagtatggcg gccagggctc cgaccctgcc gatgtggacc 240
tcggccgcga ccacgct
<210> 208
<211> 257
<212> DNA
<213> Homo sapiens
<400> 208
agcqtggtcg cggccgaggt ccacatcggc agggtcggag ccctggccgc catactcgaa 60
ctggaatcca teggteatge tetegeegaa ecagacatge etettgteet tggggttett 120
gctgatgtac cagttettet gggccacact gggctgagtg gggtacacge aggteteace 180
agtetecatg ttgcagaaga etttgatgge atccaggttg cageettggt tggggacetg 240
cccgggcggc cgctcga
<210> 209
<211> 747
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 453, 538, 540, 542, 546, 554, 556, 598, 659, 670, 679, 689,
693, 711, 723, 724, 731, 747
<223> n = A, T, C or G
<400> 209
tegageggee geoegggeag gtecaceaca cecaatteet tgetggtate atggeageeg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
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ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagcccctg 240
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cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatctt tgaggaacat ggntttaggc ggaccacacc gcccacaacg 480
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tetgtggcac ttgatgaaaa ccettacagt teagggttet ggaactttta ceaggeeint 660
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<210> 210
<211> 872
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> 165, 174, 181, 256, 260, 269, 271, 277, 286, 289, 294, 298,
300, 301, 303, 308, 311, 321, 325, 328, 329, 333, 338, 342,
346, 349, 351, 357, 359, 364, 366, 379, 385, 395, 396, 397,
407, 408, 410, 414, 415, 429, 431, 434, 435, 440, 443
<223> n = A, T, C or G
<221> misc feature
<222> 444, 446, 447, 448, 449, 450, 451, 464, 470, 472, 475, 479,
483, 484, 485, 488, 494, 496, 497, 504, 508, 509, 511, 513, 517, 522, 524, 526, 532, 533, 542, 543, 553, 559, 566, 567,
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571, 572, 578, 582, 588, 591, 594, 595, 596, 600, 606
<223> n = A, T, C or G
<221> misc feature
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664, 666, 671, 673, 678, 679, 681, 688, 690, 691, 698, 706,
707, 708, 714, 719, 721, 723, 726, 741, 751, 761, 762, 769,
770, 778, 779, 781, 782, 785, 791, 802, 807, 808, 812
<223> n = A, T, C or G
<221> misc feature
<222> 815, 820, 827, 828, 838, 841, 844, 851, 857, 864, 866, 869,
<223> n = A, T, C or G
<400> 210
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catcatggag agtggggcca aaggctgcga ggttgtggtg tctgngaaac tccnaggaca 180
ngagggctaa attccatgaa gtttgtggat ggcctgatga tccacaatcg gagacctgt 240
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ntnettgnee nteettgggt ngaanatnna atngeetnee enttentane netaetngnt 360
ccananttgg cctttaaana atccnccttg ccttnnncac tgttcanntn tttnntcgta 420
aaccctatna nttnnattan atnntnnnn nctcacccc ctcntcattn anccnatang 480
ctnnnaantc cttnanncct cccncccnnt nenctentac tnantnettc tnncccatta 540
cnnagetett tentttaana taatgnngee nngetetnea thtetaenat htgnnnaath 600
cccccnccc cnancqnntt tttgacctnn naacctcctt tcctcttccc tncnnaaatt 660
nennanttee nentteenne nttteggntn nteceatnet tteeannnet teantetane 720
ncnctncaac ttatttcct ntcatccctt nttctttaca nnccccctnn tctactcnnc 780
nnttncatta natttgaaac tnccacnnct anttncctcn ctctacnntt ttattttncg 840
ntenetetae ntaatanttt aatnanttnt en
<210> 211
<211> 517
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 462, 464, 506
<223> n = A, T, C or G
<400> 211
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tateteatet ttgggtteca caatgeteae gtggteagge aggggettet tagggeeaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
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accacaacct cgcagccttt ggccccactc tccatgatga accgcagcac accatagcag 420
gccctccgca caagcaagcc ctcctaagaa tttgtaacgc ananactctg ctggcaatgg 480
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<210> 212
<211> 695
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> 432, 476, 522, 547, 621, 624, 647, 679
<223> n = A, T, C or G
<400> 212
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gattcacaga ttccaggggg gccaggagaa ccaggggacc ctggttgtcc tggaatacca 180
gggtcaccat ttctcccagg aataccagga gggcctggat ctcccttggg gccttgaggt 240
ccttgaccat taggagggcg agtaggagca gttggaggct gtgggcaaac tgcacaacat 300
tctccaaatg gaatttctgg gttggggcag tctaattctt gatccgtcac atattatgtc 360
ategeagaga aeggateetg agteaeagae acatatttgg catggttetg getteeagae 420
atetetatee gneataggae tgaccaagat gggaacatee teetteaaca agettnetgt 480
tgtgccaaaa ataatagtgg gatgaagcag accgagaagt anccagctcc cctttttgca 540
caaagcntca tcatgtctaa atatcagaca tgagacttct ttgggcaaaa aaggagaaaa 600 '
agaaaaagca gttcaaagta nccnccatca agttggttcc ttgcccnttc agcacccggg 660
ccccqttata aaacacctng ggccggaccc ccctt
                                                                   695
<210> 213
<211> 804
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 552, 555, 592, 624, 629, 633, 658, 695, 697, 698, 700, 702,
745, 753, 755, 762, 773, 786, 788, 793, 795
<223> n = A, T, C or G
<400> 213
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gatatttaga catgatgage tttgtgcaaa aggggagetg getaettete getetgette 180
atcccactat tattttggca caacaggaag ctgttgaagg aggatgttcc catcttggtc 240
agtoctatgo ggatagagat gtotggaago cagaaccatg coaaatatgt gtotgtgact 300
caggatccgt tototgcgat gacataatat gtgacgatca agaattagac tgccccaacc 360
cagaaattcc atttggagaa tgttgtgcag tttgcccaca gcctccaact gctcctactc 420
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cccctggaat enggngaate atgccctact ggtcctcaaa ctattctccc anatgattca 600
tatgatgtca agtctgggat agcnagtang ganggactcg caggctattc tggaccanac 660
ctgccggggg ggcgttcgaa agcccgaatc tgcananntn cnttcacact ggcggccgtc 720
gagctgcttt aaaagggcca ttccnccttt agngnggggg antacaatta ctnggcggcg 780
ttttanancg cgngnctggg aaat
<210> 214
<211> 594
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 452, 509, 585
<223> n = A, T, C or G
<400> 214
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gctgatgtac cagttcttct gggccacact gggctgagtg gggtacacgc aggtctcacc 180
agticticatg ttgcagaaga ctttgatggc atccaggttg cagccttggt tggggtcaat 240
ccaqtactct ccactcttcc agtcaqagtg qcacatcttg aggtcacggc aggtgcgqqc 300
ggggttettg eggetgeeet etgggeteeg gatgtteteg atetgetgge teaggetett 360
gagggtggtg tecacetega ggteaeggte aegaaceaea ttggeateat eageeeggta 420
gtagcggcca ccatcgtgag ccttctcttg angtggctgg ggcaggaact gaagtcgaaa 480
ccagcgctgg gaggaccagg gggaccaana ggtccaggaa gggcccgggg gggaccaaca 540
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<210> 215
<211> 590
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9
<223> n = A, T, C or G
<400> 215
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ttcctgcccc agccacctca agagaaggct cacgatggtg gccgctacta ccgggctgat 180
gatgccaatg tggttcgtga ccgtgacctc gaggtggaca ccaccctcaa gagcctgagc 240
cagcagateg agaacateeg gageecagag ggcageegca agaaceeege eegcacetge 300
cgtgacctca agatgtgcca ctctgactgg aagagtggag agtactggat tgaccccaac 360
caaggctgca acctggatgc catcaaagtc ttctgcaaca tggagactgg tgagacctgc 420
gtgtacccca ctcagcccag tgtggcccag aagaactggt acatcagcaa gaaccccaag 480
gacaagaggc atgtctggtt cggcgagagc atgaccgatg gattccagtt cgagtatggc 540
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<210> 216
<211> 801
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 2, 22, 25, 26, 328, 373, 385, 440, 473, 534, 571, 572, 573,
582, 587, 589, 593, 600, 605, 617, 633, 642, 653, 672, 681,
685, 696, 699, 709, 715, 717, 726, 731, 739, 742, 745, 758,
769, 772, 778, 780, 788, 789, 791, 793, 796
<223> n = A, T, C or G
<400> 216
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agggtgctcg tggtttccct ggaactcctg gacttcctgg cttcaaaggc attaggggac 180
acaatggtct ggatggattg aagggacagc ccggtgctcc tggtgtgaag ggtgaacctg 240
gtqcccctgg tqaaaatgga actccaggtc aaacaggagc ccgtgggctt cctggtqaqa 300
gaggaccgtg ttggtgcccc tggcccanac ctcggccgcg accacgctaa gcccgaattt 360
ccagcacact ggnggccgtt actantggat ccgagctcgg taccaagctt ggcgtaatca 420
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ttaantqaaa tccqccnacc cccqgqqaaa agncqgtttg cngtattgqq qcnctttttc 660
cettteeteg gnttaettga nttantggge tttggnegnt tegggttgng geganenggt 720
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aaaacatnng ncnaangggc t
<210> 217
<211> 349
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 10, \overline{1}57, 170
<223> n = A, T, C or G
<400> 217
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gcccacgggc tectgtttga cctggagttc cattttcacc aggggcacca ggttcaccct 120
teacaceagg ageaeeggge tgteeettea atceatneag accattgtgn cecetaatge 180
etttgaagee aggaagteea ggagtteeag ggaaaceace gageaceetg tggteeaaca 240
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ggaggaccag caggaccagc gttaccaacc tgcccgggcg gccgctcga
                                                                    349
<210> 218
<211> 372
<212> DNA
<213> Homo sapiens
<400> 218
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aaageetaag caetggeaca acagtttaaa geetgattea gacattegtt eecacteate 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgeccaeggt aacaacetet teeegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcggc 360
cgcgaccacg ct
<210> 219
<211> 374
<212> DNA
<213> Homo sapiens
<400> 219
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aacqaaggct tgaaccaacc tacggatgac tcgtgctttg acccctacac agtttcccat 180
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tgcttaggct ttggaagtgg tcatttcaag atgtgattca tctagatggt gccatgacaa 300
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ggccggccgc tcga
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<210> 220
<211> 828
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9, 557, 571, 587, 588, 601, 642, 643, 647, 654, 664, 681,
688, 698, 719, 720, 725, 734, 738, 743, 744, 757, 765, 773,
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778, 780, 782, 783, 793, 798, 805, 809, 822, 827 <223> n = A, T, C or G<400> 220 tegagegnne geeegggeag gteeagtagt geetteggga etgggtteae eeceaggtet 60 geggeagttg teacagegee ageecegetg geetecaaag catgtgeagg ageaaatgge 120 accgagatat teettetgee actgttetee täegtggtat gtetteeeat categtaaca 180 cgttgcctca tgagggtcac acttgaattc tccttttccg ttcccaagac atgtgcagct 240 catttggctg gctctatagt ttggggaaag tttgttgaaa ctgtgccact gacctttact 300 tecteettet etactggage tttegtacet tecaettetg etgttggtaa aatggtggat 360 cttctatcaa tttcattgac agtacccact tctcccaaac atccagggaa atagtgattt 420 cagagogatt aggagaacca aattatgggg cagaaataag gggcttttcc acaggttttc 480 ctttggagga agatttcagt ggtgacttta aaagaatact caacagtgtc ttcatcccca 540 tagcaaaaga agaaacngta aatgatggaa ngcttctgga gatgccnnca tttaagggac 600 neceagaact teaceateta caggacetae tteagtttae annaagneae atantetgae 660 tcanaaagga cccaagtagc nccatggnca gcactttnag cctttcccct ggggaaaann 720 ttacnttett aaaneetngg eenngaeece ettaagneea aattntggaa aantteentn 780 828 cnnctggggg gengttenac atgentttna agggeceaat tneecent <210> 221 <211> 476 <212> DNA <213> Homo sapiens <400> 221 tcgagcggcc gcccgggcag gtgtcggagt ccagcacggg aggcgtggtc ttgtagttgt 60 tctccqqctq cccattqctc tcccactcca cqqcqatqtc qctqqqataq aaqcctttqa 120 ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtgt 180 acacctgtgg ttctcggggc tgccctttgg ctttggagat ggttttctcg atgggggctg 240 ggagggettt gttggagace ttgcacttgt acteettgee atteageeag teetggtgea 300 ggacggtgag gacgctgacc acacggtacg tgctgttgta ctgctcctcc cgcggctttg 360 tettggcatt atgcacetee acgeegteea egtaceagtt gaacttgace teagggtett 420 cgtggctcac gtccaccacc acgcatgtaa cctcagacct cggccgcgac cacgct <210> 222 <211> 477 <212> DNA <213> Homo sapiens <400> 222 agcgtggtcg cggccgaggt ctgaggttac atgcgtggtg gtggacgtga gccacgaaga 60 ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120 gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca 180 ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc 240 ccccatcgag aaaaccatct ccaaagccaa agggcaagcc ccgagaacca caggtgtaca 300 ccctgcccc atcccgggag gagatgacca agaaccaggt cagcctgacc tqcctggtca 360 aaggetteta teecagegae ategeegtgg agtgggagag caatgggeag eeggagaaca 420 actacaagac cacqcctccc qtqctggact ccgacacctq cccqqqcqqc cqctcqa <210> 223 <211> 361 <212> DNA <213> Homo sapiens <400> 223 tegageggee geeegggeag gttgaatgge teetegetga ceaeceeggt getggtggtg 60 ggtacagagc teegatgggt gaaaccattg acatagagac tgteeetgte cagggtgtag 120 gggcccagct cagtgatgcc gtgggtcagc tggctcagct tccagtacag ccgctctctg 180

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geoceatect teteaggest gageaaggte agtetgeaac cagagtacag agagetgaca 300
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<211> 361
<212> DNA
<213> Homo sapiens
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acagagagcg gctgtactgg aagctgagcc agctgaccca cggcatcact gagctgggcc 240
cctacaccct ggacagggac agtctctatg tcaatggttt cacccatcgg agctctgtac 300
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<211> 766
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> 574, 610, 631, 643, 657, 660, 666, 688, 712, 735, 747
\langle 223 \rangle n = A, T, C or G
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<211> 364
<212> DNA
<213> Homo sapiens
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cgct
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 <211> 275
 <212> DNA
 <213> Homo sapiens
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 <210> 228
 <211> 275
 <212> DNA
 <213> Homo sapiens
 <400> 228
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 gctcaactct cttgtccacc ttggtgttgc tgggcttgtg atctacqttg caggtgtagg 180
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 <210> 229
 <211> 40
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 1, 4, 5, 13, 15, 17, 29
 <223> n = A, T, C \text{ or } G
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                                                                 40
 <210> 230
 <211> 208
 <212> DNA
 <213> Homo sapiens
 <400> 230
agogtggtog oggoogaggt cotcacttgo otcotgcaaa gcaccgatag otgogototg 60
 tttgcgaatc agaagttcag tggacttctg ataacgtcta atttcacgga gcgccacagt 180
 accaggacct gcccgggcgg ccgctcga
 <210> 231
 <211> 208
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> 33
 <223> n = A, T, C or G
```

```
<400> 231
tegageggee geeegggeag gteetggtae tgnggegete egtgaaatta gaegttatea 60
gaaqtccact qaacttctqa ttcqcaaact tcccttccaq cqtctqqtqc qaqaaattqc 120
tcaggacttt aaaacagatc tgcgcttcca qagcgcagct atcggtgctt tgcaggaggc 180
aagtgaggac ctcggccgcg accacgct
<210> 232
<211> 332
<212> DNA
<213> Homo sapiens
<400> 232
tegageggee geeegggeag gtecacateg geagggtegg agecetggee gecatacteg 60
aactggaatc categgtcat getetegeeg aaccagacat geetettgte ettggggtte 120
ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagteteca tgttgcagaa gactttgatg gcatecaggt tgcagcettg gttggggtca 240
atccagtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
geggggttet tgaectegge egegaecaeg et
                                                                   332
<210> 233
<211> 415
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 6, 15, 19, 21
<223> n = A, T, C \text{ or } G
<400> 233
gtgggnttga accentttna netecgettg gtacegaget eggateeact agtaaeggee 60
gccagtgtgc tggaattcgg cttagcgtgg tcgcggccga ggtcaagaac cccgcccgca 120
cctgccgtga cctcaagatg tgccactctg actggaagag tggagagtac tggattgacc 180
ccaaccaagg ctgcaacctg gatgccatca aagtcttctg caacatggag actggtgaga 240
cctgcgtgta ccccactcag cccagtgtgg cccagaagaa ctggtacatc agcaagaacc 300
ccaaggacaa gaggcatgtc tggttcggcg agagcatgac cgatggattc cagttcgagt 360
atggcggcca gggctccgac cctgccgatg tggacctgcc cgggcggccg ctcga
<210> 234
<211> 776
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 505, 550, 574, 601, 604, 608, 612, 649, 656, 657, 680, 711,
750, 776
<223> n = A, T, C or G
<400> 234
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
totacagota coatcagogg cottaaacot ggagttgatt ataccatoac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagag taaccaccac tcccaaaaat 360
ggaccaggac caacaaaaac taaaactgca ggtccagatc aaacagaaat gactattgaa 420
ggcttgcagc ccacagtgga gtatgtggtt aagtgtctat gctcagaatc caagcggaga 480
```

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gaagtcagcc tctggttcag actgnaagta accaacattg atcgcctaaa ggactggcat 540
tcactgatgn ggatgccgat tccatcaaaa ttgnttggga aaacccacag gggcaagttt 600
ncangtonag gnggacotac togagocotg aggatggaat cottgactnt toottnnoot 660
gatggggaaa aaaaaccttn aaaacttgaa ggacctgccc gggcggccgt ncaaaaccca 720
attccaccc cttgggggcg ttctatgggn cccactcgga ccaaacttgg ggtaan
<210> 235
                                ١
<211> 805
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 637, 684, 705, 724, 733, 756, 778, 793, 796, 804
<223> n = A, T, C or G
<400> 235
tcgagcggcc gcccgggcag gtccttgcag ctctgcagtg tcttcttcac catcaggtgc 60
agggaatage teatggatte cateeteagg getegagtag gteaccetgt acctggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg gcatccacat cagtgaatgc 180
cagteettta gggegateaa tgttggttae tgeagtetga accagagget gaetetetee 240
qcttgqattc tqaqcataqa cactaaccac atactccact qtqqqctqca aqccttcaat 300
agtcatttct gtttgatctg gacctgcagt tttagttttt gttggtcctg gtccattttt 360
gggagtggtg gttactctgt aaccagtaac aggggaactt gaaggcagcc acttgacact 420
aatgctgttg tcctgaacat cggtcacttg catctgggat ggtttgtcaa tttctgttcg 480
gtaattaatg gaaattggct tgctgcttgc ggggcttgtc tccacggcca gtgacagcat 540
acacagtgat ggtataatca actccaggtt taagccgctg atggtagctg aaactttgct 600
ccaggcacaa gtgaactcct gacagggcta tttcctnctg ttctccgtaa gtgatcctgt 660
aatatctcac tgggacagca ggangcattc caaaacttcg ggcgngaccc cctaagccga 720
attntgcaat atncatcaca ctggcgggcg ctcgancatt cattaaaagg cccaatcncc 780
cctataggga gtntantaca attng
<210> 236
<211> 262
<212> DNA
<213> Homo sapiens
<400> 236
tegageggee geeegggeag gleactiting gittinggte atgiteggtt ggicaaagat 60
aaaaactaag tttgagagat gaatgcaaag gaaaaaaata ttttccaaag tccatgtgaa 120
attgtctccc atttttttgg cttttgaggg ggttcagttt gggttgcttg tctgtttccg 180
ggttgggggg aaagttggtt gggtgggagg gagccaggtt gggatggagg gagtttacag 240
gaagcagaca gggccaacgt cg
<210> 237
<211> 372
<212> DNA
<213> Homo sapiens
<400> 237
agcgtggtcg cggccgaggt cctcaccaga ggtgccacct acaacatcat agtggaggca 60
ctgaaagacc agcagagca taaggttcgg gaagaggttg ttaccqtqqg caactctgtc 120
aacgaagget tgaaccaace tacggatgac tegtgetttq acceetacac aqttteccat 180
tatgccqttq qaqatqaqtq qqaacqaatq tctqaatcaq qctttaaact qttqtqccaq 240
tgcttaggct ttggaaqtgg tcatttcaga tgtgattcat ctagatggtg ccatgacaat 300
ggtgtgaact acaagattgg agagaagtgg gaccgtcagg gagaaaatgg acctgcccgg 360
gcggccgctc ga
```

```
<210> 238
<211> 372
<212> DNA
<213> Homo sapiens
<400> 238
tcgagcggcc gcccgggcag gtccattttc tccctgacgg tcccacttct ctccaatctt 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgeccaeggt aacaacetet teeegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcggc 360
cgcgaccacg ct
<210> 239
<211> 720
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 478, 557, 563, 566, 620, 660, 663, 672, 673, 684, 693, 695
<223> n = A, T, C \text{ or } G
<400> 239
tegageggee geeegggeag gteeaceata agteetgata caaceaegga tgagetgtea 60
ggagcaaggt tgatttettt cattggteeg gtetteteet tgggggteae eegeactega 120
tatecagtga getgaacatt gggtggtgte caetgggege teaggettgt gggtgtgace 180
tgagtgaact tcaggtcagt tggtgcagga atagtggtta ctgcagtctg aaccagaggc 240
tgactctctc cgcttggatt ctgagcatag acactaacca catactccac tgtgggctgc 300
aageetteaa tagteattte tgtttgatet ggacetgeag ttttagtttt tgttggteet 360
ggtccatttt tgggagtggt ggttactctg taaccagtaa caggggaact tgaaggcagc 420
cacttgacac taatgctgtt gtcctgaaca tcggtcactt gcatctggga tggtttgnca 480
atttctgttc ggtaattaat ggaaattggc ttgctgcttg cggggctgtc tccacggcca 540
gtgacagcat acacagngat ggnatnatca actccaagtt taaggccctg atggtaactt 600
taaacttgct cccagccagn gaacttccgg acagggtatt tettetggtt ttccgaaagn 660
gancetggaa tnnteteett ggancagaag ganenteeaa aacttgggee ggaaceeett 720
<210> 240
<211> 691
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 564, 582, 640, 651, 666, 669, 690
<223> n = A, T, C or G
<400> 240
agegtggteg eggeegaggt cetgteagag tggeactggt agaagtteea ggaaccetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca gaagtgccag 300
gaagetgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgtctgtc tttttccttc caatcagggg ctcgctcttc tgattattct 480
```

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tcagggcaat gacataaatt gtatattcgg ttcccggttc caggccagta atagtagcct 540
cttgtgacac caggcggggc ccanggacca cttctctggg angagaccca gcttctcata 600
cttgatgatg taacceggta atcctgcacg tggcggctgn catgatacca ncaaggaatt 660
gggtgnggng gacctgcccg gcggccctcn a
<210> 241
<211> 808
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 680, 715, 721, 728, 735, 749, 757, 762, 772, 776, 779, 781,
792, 796, 800, 808
<223> n = A, T, C or G
<400> 241
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tetacageta ecateagegg cettaaacet ggagttgatt ataceateae tgtgtatget 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
gaaattqaca aaccatccca qatqcaaqtq accqatqttc aqqacaacaq cattaqtqtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagag taaccaccac tcccaaaaat 360
ggaccaggac caacaaaaac taaaactgca ggtccagatc aaacagaaat gactattgaa 420
ggcttgcagc ccacagtgga gtatgtggtt agtgtctatg ctcagaatcc aagcggagag 480
agtcagcctc tggttcagac tgcagtaacc actattcctg caccaactga cctgaagttc 540
actcaggtca cacccacaag cctgagccgc cagtggacac cacccaatgt tcactcactg 600
gatatcgagt gcgggtgacc cccaaggaga agacccggac ccatgaaaga aatcaacctt 660
gctcctgaca gctcatccgn gggtgtatca ggacttatgg gggactgccc cggcnggccg 720
ntegaaaneg aattntgaaa ttteettene aetgggngge gnttegaget tnettntana 780
nggcccaatt cncctntagn gggtcgtn
<210> 242
<211> 26
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 22
<223> n = A, T, C or G
<400> 242
                                                                   26
agcgtggtcg cggccgaggt cnagga
<210> 243
<211> 697
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 496, 541, 624, 662, 679, 688
<223> n = A, T, C \text{ or } G
<400> 243
tcgagcggcc gcccgggcag gtccaccaca cccaattcct tgctggtatc atggcagccg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
```

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gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagcccctg 240
attggaagga aaaagacaga cqaqcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agacceettt egteacceae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatett tgaggaacat ggttttagge ggaccacace geecacaaeg 480
ggcaccccca taaggnatag gccaagacca taccccgccg aatgtaggac aagaagctct 540
nteteaacaa ceateteatg ggeeceatte caggacaett etgagtaeat cattteatgt 600
catcctggtg ggcacttgat gaanaaccct tacagttcag ggttcctgga acttctacca 660
gngccacttc tgacagganc ttgggcgnga ccaccct
<210> 244
<211> 373
<212> DNA
<213> Homo sapiens
<400> 244
agogtggtcg cggccgaggt ccattttctc cctgacggtc ccacttctct ccaatcttgt 60
agttcacacc attgtcatgg caccatctag atgaatcaca tctgaaatga ccacttccaa 120
agectaagea etggeacaac agtttaaage etgatteaga cattegttee cacteatete 180
caacggcata atgggaaact gtgtaggggt caaagcacga gtcatccgta ggttggttca 240
agcettegtt gacagagttg cecaeggtaa caacetette eegaacetta tgeetetget 300
ggtctttcag tgcctccact atgatgttgt aggtggcacc tctggtgagg acctgcccgg 360
gcggcccgct cga
<210> 245
<211> 307
<212> DNA
<213> Homo sapiens
<400> 245
agegtggteg eggeegaggt gtgeeceaga ceaggaatte ggettegaeg ttggeeetgt 60
etgetteetg taaacteect ceateceaac etggeteect eccaeceaac caacttteec 120
cccaacccgg aaacagacaa gcaacccaaa ctgaaccccc tcaaaagcca aaaaaatggg 180
agacaatttc acatggactt tggaaaatat ttttttcctt tgcattcatc tctcaaactt 240
agtttttatc tttgaccaac cgaacatgac caaaaaccaa aagtgacctg cccgggcggc 300
cgctcga
<210> 246
<211> 372
<212> DNA
<213> Homo sapiens
<400> 246
tegageggee geeegggeag gteeteacea gaggtgeeae etacaacate atagtggagg 60
cactgaaaga ccagcagagg cataaggttc gggaagaggt tgttaccgtg ggcaactctg 120
tcaacgaagg cttgaaccaa cctacggatg actcgtgctt tgacccctac acagtttccc 180
attatgccgt tggagatgag tgggaacgaa tgtctgaatc aggctttaaa ctgttgtgcc 240
agtgcttagg ctttggaagt ggtcatttca gatgtgattc atctagatgg tgccatgaca 300
atggtgtgaa ctacaagatt ggagagaagt gggaccgtca gggagaaaat ggacctcggc 360
cgcqaccacq ct
                                                                  372
<210> 247
<211> 348
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> 284, 297, 299, 322, 325, 338, 342, 345
\langle 223 \rangle n = A, T, C or G
<400> 247
tcgagcggcc gcccgggcag gtaccggggt ggtcagcgag gagccattca cactgaactt 60
caccatcaac aacctgcggt atgaggagaa catgcagcac cctggctcca ggaagttcaa 120
caccacggag agggtccttc agggcctgct caggtccctg ttcaagagca ccagtgttgg 180
ccctctgtac tctggctgca gactgacttt gctcagacct gagaaacatg gggcagccac 240
tggagtggac gccatctgca ccctccgcct tgatcccact ggtnctggac tggacanana 300
geggetatac ttgggagetg ancenaacet ttggeggnga encenett
<210> 248
<211> 304
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 125
<223> n = A, T, C or G
gaggactggc tcagctccca gtatagccgc tctctgtcca gtccaggacc agtgggatca 60
aggeggaggg tgcagatggc gtccactcca gtggctgccc catgtttctc aagtctgagc 120
aaagncagtc tgcagccaga gtacagaggg ccaacactgg tgctcttgaa cagggacctg 180
agcaggccct gaaggaccct ctccqtqqtq ttqaacttcc tqqaqccaqq qtqctqcatq 240
ttctcctcat accgcaggtt gttgatggtg aagttcagtg tgaatggctc ctcgctgacc 300
accc
<210> 249
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 308, 310, 312, 320, 331, 336, 383, 392, 396
<223> n = A, T, C or G
<400> 249
agcgtggtcg cggccgaggt ccaccacac caatteettg ctggtateat ggcageegee 60
acgtgccagg attaccggct acatcatcaa gtatgagaag cctgggtctc ctcccagaga 120
agtggtccct cggccccgcc ctggtgtcac agaggctact attactggcc tggaaccggg 180
aaccgaatat acaatttatg tcattgccct gaagaataat cagaagagcg agcccctgat 240
tggaaggaaa aagacagacg agcttcccca actggtaacc cttccacacc ccaatcttca 300
tggaccanan ancttggatn gtcctttcac nggttnaaaa aacccttttc gccccccac 360
cttggggatt aaccttggga aanggggatt tnaccnttcc
                                                                    400
<210> 250
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 338, 357, 361, 369, 388, 394
<223> n = A, T, C or G
```

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<400> 250
tegageggee geeegggeag gteetgteag agtggeactg gtagaagtte caggaaceet 60
qaactqtaaq qqttcttcat caqtqccaac aqqatqacat qaaatqatqt actcaqaaqt 120
gtcctggaat ggggcccatg agatggttgt ctgagagaga gcttcttgtc ctacattcqq 180
egggtatggt ettggeetat geettatggg ggtggeegtt gtgggeggtg tggteegeet 240
aaaaccatgt tootcaaaga toatttgttg cocaacactg ggttgetgac cagaagtgcc 300
aggaagetga ataccattte cagtgteata eccagggngg gtgaccaaag ggggtenttt 360
ngacctggng aaaggaacca tccaaaanct ctgncccatg
                                                                    400
<210> 251
<211> 514
<212> .DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 8, 107, 312, 338, 351, 352, 357, 363, 366, 373, 380, 405,
421, 444, 508
<223> n = A, T, C or G
<400> 251
agcgtggncg cggccgaggt ctgaggatgt aaactcttcc caggggaagg ctgaagtgct 60
gaccatggtg ctactgggtc cttctgagtc agatatgtga ctgatgngaa ctgaagtagg 120
tactgtagat ggtgaagtct gggtgtccct aaatgctgca tctccagagc cttccatcat 180
taccgtttct tcttttgcta tgggatgaga cactgttgag tattctctaa agtcaccact 240
gaaatettee teeaaaggaa aacetgtgga aaageeeett atttetgeee cataatttgg 300
ttetectaat enetetgaaa teaetatte eetggaangt ttgggaaaaa nngggenace 360
tgncantgga aantggatan aaagatccca ccattttacc caacnagcag aaagtgggaa 420
nggtaccgaa aagctccaag taanaaaaag gagggaagta aaggtcaagt gggcaccagt 480
ttcaaacaaa actttcccca aactatanaa ccca
<210> 252
<211> 501
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 20, \overline{2}1, 25, 44, 343, 347, 356, 362, 387, 391, 398, 409, 428,
430, 453, 494
<223> n = A, T, C or G
<400> 252
aagcggccgc ccgggcaggn ncagnagtgc cttcgggact gggntcaccc ccaggtctqc 60
ggcagttgtc acagegccag eccegetggc etecaaagca tgtgcaggag caaatggcae 120
cgagatattc cttctgccac tgttctccta cgtggtatgt cttcccatca tcgtaacacg 180
ttgcctcatg agggtcacac ttgaattctc cttttccgtt cccaagacat gtgcagctca 240
tttggctggc tctatagttt ggggaaagtt tgttgaaact gtgccactqa cctttacttc 300
ctccttctct actggagctt tccgtacctt ccacttctgc tgntggnaaa aagggnggaa 360
cntcttatca atttcattgg acagtanccc nctttctncc caaaacatnc aagggaaaat 420
attgattncn agagcggatt aaggaacaac ccnaattatg ggggccagaa ataaaggggg 480
cttttccaca ggtnttttcc t
                                                                    501
<210> 253
<211> 226
<212> DNA
<213> Homo sapiens
```

```
<400> 253
tcgagcggcc gcccgggcag gtctgcagqc tattgtaagt gttctgagca catatgagat 60
aacctgggcc aagctatgat gttcgatacg ttaggtgtat taaatgcact tttgactgcc 120
atctcagtgg atgacagcct tctcactgac agcagagatc ttcctcactg tgccagtggg 180
caggagaaag agcatgctgc gactggacct cggccgcgac cacgct
<210> 254
<211> 226
<212> DNA
<213> Homo sapiens
<400> 254
agcgtggtcg cggccgaggt ccagtcgcag catgctcttt ctcctgccca ctggcacagt 60
gaggaagatc tctgctgtca gtgagaaggc tgtcatccac tgagatggca gtcaaaagtg 120
catttaatac acctaacgta tcgaacatca tagcttggcc caggttatct catatgtgct 180
cagaacactt acaatagcct gcagacctgc ccgggcggcc gctcga
                                                                  226
<210> 255
<211> 427
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 327, 403
<223> n = A, T, C or G
<400> 255
cgagcggccg cccgggcagg tccagactcc aatccagaga accaccaagc cagatgtcag 60
aagctacacc atcacaggtt tacaaccagg cactgactac aagatctacc tgtacacctt 120
gaatgacaat gctcggagct cccctgtggt catcgacgcc tccactgcca ttgatgcacc 180
atccaacctg cgtttcctgg ccaccacac caattccttg ctggtatcat ggcagccgcc 240
acgtgccagg attaccggct acatcatcaa gtatgagaag cctgggtctc ctcccagaga 300
agtggtccct cggccccgcc ctggtgncac agaagctact attactggcc tggaaccggg 360
aaccgaatat acaatttatg tcattgccct qaagaataat canaagagcg agcccctgat 420
tggaagg
<210> 256
<211> 535
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 347, 456, 475
<223> n = A, T, C or G
<400> 256
agcgtggtcg cggccgaggt cctgtcagag tggcactggt agaagttcca ggaaccctga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct gtctttttcc 180
ttccaatcag gggctcgctc ttctgattat tcttcagggc aatgacataa attgtatatt 240
cggttcccgg ttccaggcca gtaatagtag cctctgtgac accagggcgg ggccgaggga 300
ccacttctct gggaggagac ccaggcttct catacttgat gatgtanccg gtaatcctgg 360
caccgtggcg gctgccatga taccagcaag gaattgggtg tggtggccaa gaaacgcagg 420
ttggatggtg catcaatggc agtggaggcg tcgatnacca caggggagct ccgancattg 480
tcattcaagg tggacaggta gaatcttgta atcaggtgcc tggtttgtaa acctg
                                                                  535
```

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<210> 257
<211> 544
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 495, 511
<223> n = A, T, C or G
<400> 257
tegageggee geeegggeag gtttegtgae egtgaeeteg aggtggaeae cacceteaag 60
agcctgagcc agcagatcga gaacatccgg agcccagagg gcagccgcaa gaaccccgcc 120
cgcacctgcc gtgacctcaa gatgtgccac tctgactgga agagtggaga gtactggatt 180
gaccccaacc aaggetgcaa cetggatgce atcaaagtet tetgcaacat ggagactggt 240
gagacetgeg tgtaceceae teageeeagt gtggeeeaga agaactggta cateageaag 300
aaccccaagg acaagaagca tgtctggttc ggcgaaagca tgaccgatgg attccagttc 360
gagtatggcg gccagggctc cgaccctgcc gatgtggacc tcggccgcga ccacgctaag 420
cccgaattcc agcacactgg cggccgttac tagtgggatc cgagcttcgg taccaagctt 480
ggcgtaatca tgggncatag ctgtttcctg ngtgaaaatg gtattccgct tcacaatttc 540
                                                                   544
ccac
<210> 258
<211> 418
<212> DNA
<213> Homo sapiens
<400> 258
agegtggteg eggeegaggt ceacategge agggteggag ecetggeege catactegaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
gctgatgtac cagttcttct gggccacact gggctgagtg gggtacacgc aggtctcacc 180
agtctccatg ttgcagaaga ctttgatggc atccaggttg cagccttggt tggggtcaat 240
ccagtactct ccactcttcc agtcagagtg gcacatcttg aggtcacggc aggtgcgggc 300
ggggttettg eggetgeect etgggeteeg gatgtteteg atetgetgge teaagetett 360
gaagggtggt gtccacctcg aggtcacggt cacgaaacct gcccgggcgg ccgctcga
<210> 259
<211> 377
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 320, 326, 342, 352
<223> n = A, T, C or G
<400> 259
agogtggtcg cggccgaggt caagaacccc qcccgcacct gccgtgacct caagatgtgc 60
cactctgact ggaagagtgg agagtactgg attgacccca accaaggctg caacctggat 120
gccatcaaag tcttctgcaa catggagact ggtgagacct gcgtgtaccc cactcagccc 180
agtgtggccc agaagaactg gtacatcagc aagaacccca aggacaagag gcatgtctgg 240
ttcggcgaga gcatgaccga tggattccag ttcgagtatg gcggccaggg ctccgaccct 300
geogatgtgg acctgeecgn geoggneege tegaaaagee enaattteea gneacaettg 360
gccggccgtt actactg
<210> 260
<211> 332
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<212> DNA
<213> Homo sapiens
<400> 260
tegageggee geeegggeag gtecacateg geagggtegg ageeetggee gecatacteg 60
aactggaatc catcggtcat gctctcgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
geggggttet tgacetegge egegaceaeg et
<210> 261
<211> 94
<212> DNA
<213> Homo sapiens
<400> 261
ttttttttt ttttttttt ttttttttttttt
<210> 262
<211> 650
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 412, 582, 612, 641, 646
<223> n = A, T, C or G
<400> 262
agegtggteg eggeegaggt etggeattee ttegaettet etceageega getteecaga 60
acatcacata tcactgcaaa aatagcattg catacatgga tcaggccagt ggaaatgtaa 120
agaaggccct gaagctgatg gggtcaaatg aaggtgaatt caaggctgaa ggaaatagca 180
aattcaccta cacagttctg gaggatggtt gcacgaaaca cactggggaa tggagcaaaa 240
cagtetttga atategaaca egeaaggetg tgagactace tattgtagat attgcaccet 300
atgacattgg tggtcctgat caagaatttg gtgtggacgt tggccctgtt tgctttttat 360
aaaccaaact ctatctgaaa tcccaacaaa aaaaatttaa ctccatatgt gntcctcttg 420
ttctaatctt ggcaaccagt gcaagtgacc gacaaaattc cagttattta tttccaaaat 480
gtttggaaac agtataattt gacaaagaaa aaaggatact tctctttttt tggctggtcc 540
accaaataca attcaaaagg ctttttggtt ttatttttt anccaattcc aatttcaaaa 600
tgtctcaatg gngcttataa taaaataaac tttcaccctt nttttntgat
                                                                650
<210> 263
<211> 573
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 453, 458, 544
\langle 223 \rangle n = A,T,C or G
<400> 263
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
qtcactggcc qtqgaqacag ccccqcaagc aqcaagccaa tttccattaa ttaccqaaca 240
```

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gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagaa gtaaccacca ctcccaaaaa 360
tggaccagga ccaacaaaaa ctaaaactgc aggtccagat caaacagaaa atggactatt 420
gaaggettge ageceacagt ggaagtatgt ggntaggngt etatgeteag aateceaage 480
cggagaaagt cagcettetg gtttagactg cagtaaccaa cattgatege cetaaaggac 540
tggncattca cttggatggt ggatgtccaa ttc
<210> 264
<211> 550
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 39, \overline{174}, 352, 526
<223> n = A, T, C or G
<400> 264
tegageggee geeegggeag gteettgeag etetgeagng tettetteac cateaggtge 60
agggaatage teatggatte cateeteagg getegagtag gteaccetgt acetggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagngaatgc 180
cagteettta gggegateaa tgttggttae tgeagtetga. accagagget gaetetetee 240
gcttggattc tgagcataga cactaaccac atactccact gtgggctgca agccttcaat 300
agtcatttct gtttgatctg gacctgcagt tttaagtttt tggtggtcct gncccatttt 360
tgggaagtgg ggggttactc tgtaaccagt aacaggggaa cttgaaggca gccacttgac 420
actaatgctg ttgtcctgaa catcggtcac ttgcatctgg ggatggtttt gacaatttct 480
ggttcggcaa attaatggaa attggcttgc tgcttggcgg ggctgnctcc acgggccagt 540
gacagcatac
<210> 265
<211> 596
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature <222> 347, 352, 353, 534, 555, 587
<223> n = A, T, C or G
<400> 265
tegageggee geeegggeag gteettgeag etetgeagtg tettetteae cateaggtge 60
agggaatage teatggatte cateeteagg getegagtag gteaceetgt acetggaaae 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagtgaatgc 180
cagteettta gggegateaa tgttggttac tgcagtetga accagagget gactetetee 240
gcttggattc tgagcataga cactaaccac atactccact gtgggctgca agccttcaat 300
agtcatttct gtttgatctg gacctgcagt tttaagtttt tgttggncct gnnccatttt 360
tggggaaggg gtggttactc ttgtaaccag taacagggga acttgaagca gccacttgac 420
actaatgctg gtggcctgaa catcggtcac ttgcatctgg gatggtttgg tcaattctg 480
ttcggtaatt aatgggaaat tqqcttactq qcttqcqqqq qctqtctcca cqqncaqtqa 540
caagcataca caggngatgg gtataatcaa ctccaggttt aaggccnctg atggta
<210> 266
<211> 506
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
```

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<222> 393, 473
<223> n = A, T, C or G
<400> 266
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacqqaq aaacaqqaqq aaataqccct qtccaqqaqt tcactqtqcc tggqaqcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
qtcactggcc gtggagacag ccccgcaagc agtaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagag taaccaccac tcccaaaaat 360
gggaccagga ccaacaaaaa actaaaactg canggtccag atcaaacaga aatgactatt 420
gaaggettge ageceaeagt ggagtatgtg ggttagtgte tatgeteaga atnecaageg 480
gagagagtca gcctctggtt cagact
<210> 267
<211> 548
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 346, 358, 432, 510, 512
<223> n = A, T, C \text{ or } G
<400> 267
tegageggee geeegggeag gteagegete teaggaegte accaecatgg cetgggetet 60
gctcctcctc accctcctca ctcagggcac agggtcctgg gcccagtctg ccctgactca 120
geeteectee gegteegggt eteetggaca gteagteace ateteetgea etggaaceag 180
cagtgacqtt ggtgcttatg aatttgtctc ctggtaccaa caacacccag gcaaggcccc 240
caaactcatg atttctgagg tcactaagcg gccctcaggg gtccctgatc gcttctctqq 300
ctccaagtct ggcaacacgg cctccctgac cgtctctggg ctccangctg aggatgangc 360
tgattattac tggaagctca tatgcaggca acaacaattg ggtgttcggc ggaagggacc 420
aagetgaceg tnetaaggte aageceaagg ettgeceee teggteacte tgtteecace 480
ctcctctgaa gaagctttca agccaacaan gncacactgg gtgtgtctca taagtggact 540
ttctaccc
<210> 268
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 98, \overline{3}80, 421, 454, 495, 506, 512, 561, 565, 579
<223> n = A, T, C or G
<400> 268
agcgtggtcg cggccgaggt ctgtagcttc tgtgggactt ccactgctca ggcgtcaggc 60
tcaggtagct gctggccgcg tacttgttgt tgctttgntt ggagggtgtg gtggtctcca 120
ctcccqcctt qacqqqctq ctatctqcct tccaqqccac tqtcacqqct cccqqqtaqa 180
agtcacttat gagacacacc agtgtggcct tgttggcttg aagctcctca gaggagggtg 240
ggaacagagt gaccgagggg gcagccttgg gctgacctag gacggtcagc ttggtccctc 300
cgccgaacac ccaattgttg ttgcctgcat atgagctgca gtaataatca gcctcatcct 360
cagectggag cecagagaen gteaagggag geeegtgttt geeaagaett ggaageeaga 420
naagcgatca gggacccctg agggccgctt tacngacctc aaaaaatcat gaatttgggg 480
ggcctttgcc tgggngttgg ttggtnacca gnaaaacaaa atttcataaa gcaccaacgt 540
cactgctggt ttccagtgca ngaanatggt gaactgaant gtcc
                                                                    584
```

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<210> 269
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 265, 329
<223> n = A, T, C or G
<400> 269
agogtggtcg cggccgaggt ccagcatcag gaqccccgcc ttgccgqctc tggtcatcgc 60
ctttcttttt gtggcctgaa acgatgtcat caattcgcag tagcagaact gccgtctcca 120
ctgctgtctt ataagtctgc agettcacag ccaatggctc ccatatgccc agttccttca 180
tgtccaccaa agtacccgtc tcaccattta caccccaggt ctcacagttc tcctgggtgt 240
gettggcccg aagggaggta agtanacgga tggtgctggt cccacagttc tggatcaggg 300
tacgaggaat gacctctagg gcctgggcna caagccctgt atggacctgc ccgggcgggc 360
ccgctcga
                                                                   368
<210> 270
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 54, 163, 219, 229, 316
<223> n = A, T, C or G
<400> 270
tcgagcggcc gcccgggcag gtccatacag ggctgttgcc caggccctag aggncattcc 60
ttgtaccetg atccagaact gtgggaccag caccatccgt ctacttacct ccettcgggc 120
caagcacacc caggagaact gtgagacctg gggtgtaaat ggngagacgg gtactttggt 180
ggacatgaag gaactgggca tatgggagcc attggctgng aagctgcana cttataagac 240
agcagtggag acggcagttc tgctactgcg aattgatgac atcgtttcag gccacaaaaa 300
gaaaggegat gaccanagce ggcaaggegg ggcttcctga tgctggacct cggccgccga 360
ccacgctt
                                                                   368
<210> 271
<211> 424
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 279, 329, 362, 384, 400
<223> n = A, T, C or G
<400> 271
agcgtggtcg cggccgaggt ccactagagg tctgtgtgcc attgcccagg cagagtctct 60
gcgttacaaa ctcctaggag ggcttgctgt gcggagggcc tgctatggtg tgctgcggtt 120
catcatggag agtggggcca aaggctgcga ggttgtggtg tctgggaaac tccgaggaca 180
gagggetaaa tecatgaagt ttgtggatgg cetgatgate cacageggag accetgttaa 240
ctactacgtt gacactgctg tgcgccacgt gttgctcana cagggtgtgc tgggcatcaa 300
ggtgaagatc atgctgccct gggacccanc tggcaaaaat ggcccttaaa aaccccttgc 360
cntgaccacg tgaaccattt gtgngaaccc caagatgaan atacttgccc accaccccc 420
attc
                                                                   424
```

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<210> 272
<211> 541
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 422, 442, 510, 513, 515, 525
<223> n = A, T, C or G
<400> 272
tegageggee geeegggeag gtetgeeaag gagaeeetgt tatgetgtgg ggaetggetg 60
gggcatggca ggcggctctg gcttcccacc cttctgttct gagatggggg tggtgggcag 120
tateteatet ttgggtteca caatgeteae gtggteagge aggggettet tagggeeaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacag cagtgtcaac gtagtagtta acagggtctc cgctgtggat 300
catcaggica tocacaaact toatggattt agocototgt cotoggagtt toccaaaaca 360
ccacaacctc gccagccttt gggccccact tcttcatgaa tgaaaccgca gcacaccatt 420
ancaaggeee tteegeacag gnaageeett eetaaggagt tttgtaaaeg caaaaaaete 480
ttgcctgggg caaatgggca cacagacctn tantnggacc ttggnccgcg aaccaccgct 540
<210> 273
<211> 579
<212> DNA -
<213> Homo sapiens
<220>
<221> misc feature
<222> 223, 265, 277, 308, 329, 346, 360, 366, 429, 448, 517, 524,
531, 578
<223> n = A, T, C or G
<400> 273
agegtggteg eggeegaggt etggeeetee tggeaagget ggtgaagatg gteaceetgg 60
aaaacccgga cgacctggtg agaqaggagt tgttggacca cagggtgctc gtggtttccc 120
tggaactcct ggacttcctg gcttcaaagg cattagggga cacaatggtc tggatggatt 180
gaagggacag cccggtgctc ctggtgtgaa gggtgaacct ggngcccctg gtgaaaatgg 240
aactccaggt caaacaggag cccgngggct tcctggngag agaggacgtg ttggtgcccc 300
tggcccanac ctgcccgggc ggccgctcna aaagccgaaa tccagnacac tggcggccgn 360
tactantgga atccgaactt cggtaccaaa gcttggccgt aatcatggcc atagcttgtt 420
ccctggggng gaaattggta ttccgctncc aattccacac aacataccga acccggaaag 480
cattaaagtg taaaagccct gggggggcct aaatgangtg agcntaactc ncatttaatt 540
ggcgttgcgc ttcactgccc cgcttttcca gtccgggna
                                                                   579
<210> 274
<211> 330
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 171
<223> n = A, T, C or G
<400> 274
tcgagcggcc gcccgggcag gtctgggcca ggggcaccaa cacgtcctct ctcaccagga 60
agcccacggg ctcctgtttg acctggagtt ccattttcac caggggcacc aggttcaccc 120
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ttcacaccag gagcaccggg ctgtcccttc aatccatcca gaccattgtg neccctaatg 180
cctttqaaqc caqqaaqtcc aqqaqttcca qqqaaaccac qaqcaccctq tqqtccaaca 240
actectetet caccagging teegggittit ceagggingae cateticace ageetingea 300
                                                                   330
ggagggccag acctcggccg cgaccacgct
<210> 275
<211> 97
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 2, 35, 72
<223> n = A, T, C or G
<400> 275
ancettegtce cegeceaget ceteaceaga getencacet acaacateat agtegageca 60
ctgaaagacc ancagaggca taaggttcgg gaagagg
<210> 276
<211> 610
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 358, 360, 363, 382, 424, 433, 464, 468, 477, 491, 499, 511,
558, 584, 588, 590
<223> n = A, T, C or G
<400> 276
tcgagcggcc gcccgggcag gtccattttc tccctgacgg tcccacttct ctccaatctt 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaageetaag caetggeaca acagtttaaa geetgattea gacattegtt eecacteate 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgtccacggt aacaacetet teecgaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcngn 360
congaacaac gottaagooo gnattotgoa gaataatooo atcacacttg goggoogott 420
cgancatgca tentaaaagg ggeeccaatt teeecettat aagngaanee gtatttneea 480
atttcactgg necegecgnt tttacaaacg neggtgaact ggggaaaaac eetggeggtt 540
acceaacttt aategeentt ggeageacaa teeeceettt tegneeanen tgggegtaaa 600
taaccgaaaa
                                                                   610
<210> 277
<211> 38
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 2, 5, 18, 21, 31
<223> n = A, T, C or G
<400> 277
ancgnggtcg cggccgangt nttttttttt
                                                                   38
<210> 278
<211> 443
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<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 156, 212, 233, 245, 327, 331, 336, 361, 364, 381, 391, 397,
419, 437
<223> n = A, T, C or G
<400> 278
agcgtggtcg cggccgaggt ctgaggttac atgcgtggtg gtggacgtga gccacgaaga 60
ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120
gccgcgggag gagcagtaca acagcacgta ccgggnggtc agcgtcctca ccgtcctgca 180
ccagaattgg ttgaatggca aggagtacaa gngcaaggtt tccaacaaag ccntcccagc 240
ccccntcgaa aaaaccattt ccaaagccaa agggcagccc cgagaaccac aggtgtacac 300
cctgcccca tcccgggagg aaaagancaa naaccnggtt cagccttaac ttgcttggtc 360
naangetttt tateecaacg nactteece ntggaantgg gaaaaaccaa tgggeeaane 420
cgaaaaacaa ttacaanaac ccc
                                                                   443
<210> 279
<211> 348
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 219, 256, 291, 297, 307, 314, 317
<223> n = A, T, C or G
<400> 279
tcgagcggcc gcccgggcag gtgtcggagt ccagcacggg aggcgtggtc ttgtagttgt 60
tetecggetg eccattgete teccaeteca eggegatgte getgggatag aageetttga 120
ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtga 180
acacctgggg ttctcggggc ttgccctttg gttttgaana tggttttctc gatgggggct 240
ggaagggett tgttgnaaac cttgcacttg actccttgcc attcacccag ncctggngca 300
ggacggngag gacnetnace acaeggaace gggetggtgg actgetee
<210> 280
<211> 149
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 18, 34, 51, 118, 120, 140
<223> n = A, T, C or G
<400> 280
agcqtgqtcq cqqacqanqt cctqtcaqaq tqqnactqqt agaaqttcca nqaacctqa 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagngn 120
cctggaatgg ggcccatgan atggttgcc
<210> 281
<211> 404
<212> DNA
<213> Homo sapiens
<220>
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<221> misc_feature
<222> 383, 386, 388, 393
<223> n = A, T, C or G
<400> 281
tegageggee geeegggeag gteeaceaca cecaatteet tgetggtate atggeageeg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagcccctg 240
attggaagga aaaagacaga egagetteee caactggtaa eeetteeaca eeecaatett 300
catggaccag agatettgga tgtteettee acagtteaaa agacceettt eggeaccee 360
cctgggtatg aacctgggaa aanggnantt aanctttcct ggca
<210> 282
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 320, 341, 424, 450, 459, 487, 498
<223> n = A, T, C or G
<400> 282
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acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca qatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaaggtn ccctggtact gggttacaga ntaaccacca ctcccaaaaa 360
tggaccagga accacaaaaa cttaaactgc agggtccaga tcaaaacaga aatgactatt 420
gaangettge ageceacagt gggagtatgn gggtagtgne tatgetteag aatecaageg 480
gaaaaangtc aagccttntg ggttcaa
<210> 283
<211> 325
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 216, 292, 303, 304
<223> n = A, T, C or G
<400> 283
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agggaatage teatggatte cateeteagg getegagtag gteaccetqt acetggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagtgaatgc 180
cagtccttta gggcgatcaa tgttggttac tgcagnctga accagaggct gactctctcc 240
gettggatte tgageataga cactaaceae atacteeaet gtgggetgea ancetteaat 300
aanncatttc tgtttgatct ggacc
<210> 284
<211> 331
<212> DNA
<213> Homo sapiens
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<221> misc feature $\langle 222 \rangle$ 54, $\overline{5}9$, 63, 121, 312, 327 <223> n = A, T, C or G<400> 284 tegageggee geeegggeag gtetggtggg gteetggeae acgeaeatgg gggngttgnt 60 ctnatccage tgcccagece ceattggega gtttgagaag gtgtgcagea atgacaacaa 120 nacettegae tetteetgee acttetttge cacaaagtge accetggagg geaccaagaa 180 gggccacaag ctccacctgg actacatcgg gccttgcaaa tacatccccc cttgcctgga 240 ctctgagetg accgaattcc cccttgcgca tgcgggactg gctcaagaac cgtcctggca 300 cccttgtatg anagggatga agacacnacc c <210> 285 <211> 509 <212> DNA <213> Homo sapiens <220> <221> misc feature <222> 316, 319, 327, 329, 339, 344, 357, 384, 398, 427, 443, 450, 478 <223> n = A, T, C or G<400> 285 agcgtggtcg cggccgaggt ctgtcctaca gtcctcagga ctctactccc tcagcagcgt 60 ggtgaccgtg ccctccagca acttcggcac ccagacctac acctgcaacg tagatcacaa 120 gcccagcaac accaaggtgg acaagagagt tgagcccaaa tcttgtgaca aaactcacac 180 atgcccaccg tgcccagcac etgaacteet ggggggaccg teagtettee tetteccccg 240 cateccectt ccaaacetge eegggeggee getegaaage egaatteeag cacaetggeg 300 gccggtacta gtgganccna acttggnanc caacctggng gaantaatgg gcataanctg 360 tttctggggg gaaattggta tccngtttac aattcccnca caacatacga gccggaagca 420 taaaagngta aaagcctggg ggnggcctan tgaagtgaag ctaaactcac attaattngc 480 gttgccgctc actggcccgc ttttccagc <210> 286 <211> 336 <212> DNA <213> Homo sapiens <220> <221> misc_feature <222> 188, 251, 267 <223> n = A, T, C or G<400> 286 tcgagcggcc gcccgggcag gtttggaagg gggatgcggg ggaagaggaa gactgacggt 60 cccccagga gttcaggtgc tgggcacggt gggcatgtgt gagttttgtc acaagatttg 120 ggctcaactc tettgtccac cttggtgttg ctgggcttgt gatctacgtt gcaggtgtag 180 gtctgggngc cgaagttgct ggagggcacg gtcaccacgc tgctgaggga gtagagtcct 240 gaggactgta ngacagacct cggccgngac cacgctaagc cgaattctgc agatatccat 300 cacactggcg gccgctccga gcatgcattt tagagg <210> 287 <211> 30 <212> DNA <213> Homo sapiens

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<221> misc feature
<222> 8, 18
<223> n = A, T, C or G
<400> 287
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agcgtggncg cggacganga caacaaccc
<210> 288
<211> 316
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 22, 130
<223> n = A, T, C or G
<400> 288
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aactggaatc catcggtcat gctcttgccg aaccagacat gcctcttgtc cttggggttc 120
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ccagteteca tgttgcagaa gaetttgatg gcatecaggt tgcageettg gttggggtca 240
atccagtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
gcggggttct tgacct
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<210> 289
<211> 308
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 36, 165, 191, 195, 218, 235
<223> n = A, T, C or G
<400> 289
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ggggctccgg ntganaaagg tgaaggaggc cctcctgnat tggcaggggc cccangactt 240
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ccacctgg
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<210> 290
<211> 324
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 184
<223> n = A, T, C or G
<400> 290
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tttggaccag gacttccaag acctcctctt tctccaggca ttccttgcag accaggagta 180
ccancagcac caggtggccc aggaggacca gcagcaccct ttcctccttc gggaccaggg 240
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<210> 291
<211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 249, 267
<223> n = A, T, C or G
<400> 291
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atccagaacg agaaggagac catgcaaagc ctgaacgacc gcctggcctc ttacctggac 120
agagtgagga gcctggagac cgacaaccgg aggctggaga gcaaaatccg ggagcacttg 180
gagaagaagg gaccccaggt cagagactgg agccattact tcaagatcat cgaggacctg 240
agggctcana tcttcgcaaa tactgcngac aatgcccg
<210> 292
<211> 299
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 6, 1\overline{9}, 25, 51, 53, 61, 63, 70, 109, 136, 157, 241, 276
<223> n = A, T, C or G
<400> 292
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atctgagccc tcaggncctc gatgatcttg aagtaanggc tccagtctct gacctggggt 180
coefficient coaagtgete coggattitg etetecagee teeggttete ggtetecaag 240
ncttctcact ctgtccagga aaagaggcca ggcggncgat cagggctttt gcatggact 299
<210> 293
<211> 101
<212> DNA
<213> Homo sapiens
<400> 293
ttttttttt tttttttt tttttttt ttttttt t
<210> 294
<211> 285
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 64, 103, 110, 237, 282
<223> n = A, T, C or G
<400> 294
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tctaataacg agctggttcg taccaagacc ctggtgaaga attgcatcgt gctcatngac 240
agcacaccgt accgacagtg ggtaccgaag tcccactatg cncct
<210> 295
<211> 216
<212> DNA
<213> Homo sapiens
<400> 295
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ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
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<210> 296
<211> 414
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 7, 10, 33, 61, 62, 63, 88, 109, 122, 255, 298, 307, 340,
355, 386, 393
<223> n = A, T, C or G
<400> 296
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gnccagtaat agtagcctct gtgacaccag ggcggggccg agggaccact tctctgggag 180
gagacccagg cttctcatac ttgatgatga agccggtaat cctggcacgt gggcggctgc 240
catgatacca ccaangaatt gggtgtggtg gacctgcccg ggcgggccgc tcgaaaancc 300
gaattentge aagaatatee ateacacttg ggegggeegn tegaaceatg catentaaaa 360
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<210> 297
<211> 376
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 312, 326, 335, 361
<223> n = A, T, C or G
<400> 297
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coeggecete etggacetee tggteeceet ggteeteeca gegetggttt egaetteage 120
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gatgccaatg tggttcgtga ccgtgacctc gaggtggaca ccaccctcaa gagccttgag 240
ccagcagaat cqaaaacatt cggaacccaa qaaqqqcaag cccgcaaaqa aaccccqccc 300
gcacctggcc gngaacctcc aagaangtgc ccacntcttg actgggaaaa aaaqggaaaa 360
ntacttggaa ttggac
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<210> 298
<211> 357
<212> DNA
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<213> Homo sapiens
<221> misc_feature
<222> 345, 346
<223> n = A, T, C or G
<400> 298
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ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
gctgatgtac cagttettet gggccacact gggctgagtg gggtacacgc aggteteace 180
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geggggttet tgegggetge cettetggge teeeggaatg ttetnngaae ttgetgg
<210> 299
<211> 307
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 281, 285, 306
<223> n = A, T, C or G
<400> 299
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gcgttacaaa ctcctaggag ggcttgctgt gcggagggcc tgctatggtg tgctgcggtt 120
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caaggng
<210> 300
<211> 351
<212> DNA
<213> Homo sapiens
<400> 300
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gagcaacacg tggcgcacag caagtgtcaa cgtaagtaag ttaacagggt ctccgctgtg 300
gatcatcagg ccatccacaa acttcatgga tttaaccctc tqtcctcqqa q
<210> 301
<211> 330
<212> DNA
<213> Homo sapiens
<400> 301
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gtccagggtg taggggccca gctctttgat gccattggcc agttggctca gctcccagta 180
cagccgctct ctgttgagtc cagggctttt ggggtcaaga tgatggatgc agatggcatc 240
cactccagtg gctgctccat ccttctcgga cctgagagag gtcagtctgc agccagagta 300
cagagggcca acactggtgt tctttgaata
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<210> 302-
<211> 317
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 129, 295
<223> n = A, T, C or G
<400> 302
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agetgggccc ctacaccetg gacaggaaca gtetetatgt caatggttte acceateaga 120
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ctccatcctc cctctccagc cccacaatta tggctgctgg ccctctcctg gtaccattca 240
ccctcaactt caccatcacc aacctgcagt atggggagga catgggtcac cctgnctcca 300
ggaagttcaa caccaca
                                                                     317
<210> 303
<211> 283
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 139, 146, 195
<223> n = A, T, C or G
<400> 303
tegageggee geeeggacag gtetgggegg atageaeegg geatattttg gaatggatga 60
ggtctggcac cctgagcagt ccagcgagga cttggtctta gttgagcaat ttggctagga 120
ggatagtatg cagcacggnt ctgagnctgt gggatagctg ccatgaagta acctgaagga 180
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<210> 304
<211> 72
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 59
<223> n = A, T, C or G
<400> 304
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ctgctggtcc tg
<210> 305
<211> 245
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 5, 1\overline{1}, 22, 98, 102
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<223> n = A, T, C or G
<400> 305
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                                                                   245
<210> 306
<211> 246
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 144, 159
<223> n = A, T, C or G
<400> 306
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gagaagaagg gaccccaggt caagagactg gagccattac ttcaagatca tcgagggacc 240
tggagg
<210> 307
<211> 333
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 5
<223> n = A, T, C or G
<400> 307
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ceteactety tecaggtaag aaggeecagg eggtegttea ggetttgeat ggteteette 300
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                                                                   333
<210> 308
<211> 310
<212> DNA
<213> Homo sapiens
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ttggtgatgg
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<210> 309

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<211> 429
<212> DNA
<213> Homo sapiens
<400> 309
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<211> 430
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<213> Homo sapiens
<220>
<221> misc feature
<222> 342
<223> n = A, T, C or G
<400> 310
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<212> DNA
<213> Homo sapiens
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gatetgeaat gaetggaact tgeeggtgee tggggtgeet tteeceeage cagggteeaa 2940
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<210> 312
<211> 914
<212> PRT
<213> Homo sapiens
<400> 312
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Leu Gly Pro Pro Gln Trp Thr Trp Glu His Leu Gly Leu Gln Phe Leu
Asn Leu Val Pro Arg Leu Pro Ala Leu Ser Trp Cys Tyr Ser Leu Ser
                            40
Thr Ser Pro Ser Pro Thr Cys Gly Met Arg Arg Thr Cys Ser Thr Leu
Ala Pro Gly Ser Ser Thr Pro Arg Arg Gly Ser Phe Arg Ala Trp Ser
                    70
Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu
                                   90
Thr Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr Gly Val Asp Ala
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105 Ile Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu 120

Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu

Gly Pro Tyr Ala Leu Asp Asn Asp Ser Leu Phe Val Asn Gly Phe Thr

125

140

100

· 135

His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr Pro Thr Val Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser Ile Phe Gly Pro Ser Ala Ala Ser His Leu Leu Ile Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Trp Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val Val Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Pro Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp

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610
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Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys
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                                       635
Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe
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               645
Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys
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                                                   670
Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe
                                               685
                           680
Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr
                        695
                                           700
Gln, Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln
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                                        715
Pro Thr Ser Ser Ser Thr Gln His Phe Tyr Leu Asn Phe Thr Ile
                725
                                   730
                                                       735
Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn
           740
                                745
Tyr Gln Arg Asn Lys Arg Asn Ile Glu'Asp Ala Leu Asn Gln Leu Phe
                           760
                                               765
Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr
                        775
                                           780
Phe Arg Ser Val Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys
                    790
                                       795
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
                805
                                   810
Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr
           820
                               825
Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Phe Pro Asn Arg Asn
       835
                           840
                                               845
Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu
                       855
                                           860
Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly
                    870
                                       875
Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val
                885
                                   890
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            900
                                905
Leu Gln
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<210> 313
<211> 656
<212> DNA
<213> Homo sapiens
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<400> 313

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<211> 519
<212> DNA
<213> Homo sapiens
<400> 314
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gtttaaggat ggtctcggtg gttaggccca ctagaataaa ctgagtccaa tacctctaca 180
cagttatgtt taactgggct ctctgacacc gggaggaagg tggcggggtt taggtgttgc 240
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cattcattag ctaatggtgt cctttggtat ttattaaaat caccacagca tagggggact 360
ttatgtttag gttttgtcta agagttagct tatctgcttc ttgtgctaac agggctattg 420
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<210> 315
<211> 441
<212> DNA
<213> Homo sapiens
<400> 315
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cagaggcaac cagggtttat agtgctaggt aaatgtcatc tcttttgtgc tactgactca 180
ttgtcaaacg tctctgcact gttttcagcc tctccacgtt gcctctgtcc tgcttcttag 240
ttccttcttt gtgacaaacc aaaagaataa gaggatttag aacaggactg cttttcccct 300
atgatttaaa aattocaatg actttogooc ttgggagaaa tttocaagga aatotototo 360
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<210> 316
<211> 247
<212> DNA
<213> Homo sapiens
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ccagtctagc ttggtaagaa gagagacatg cccccaacct cggcgccctt tttcctcacg 180
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<210> 317
<211> 409
<212> DNA
<213> Homo sapiens
<400> 317
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gaatgeteee tggaggeeet gtggegagga caggeaetgg atggteeaga ceetetgget 180
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ctgtcaggaa cctggccctg ggagggctca ggtgagctca caaggagagg tcaagccaag 360
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<210> 318
<211> 320
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 6, 1\overline{7}, 24, 271
<223> n = A, T, C or G
<400> 318
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gtcactgggc ctttgctcgg gaggaggcat cacccagaaa ggcgagatct tggactcggg 240
gcctgggttg ccagaatagt aaggggagca nagcagggcg aggcagggct ggaagccatt 300
gctggagccc tgcagccgca
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<210> 319
<211> 212
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 172 ,
<223> n = A, T, C or G
<400> 319
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ggcctcagag ccctggtaaa tgtgaccctt tttggggtct ttttcaaccc anacctggtc 180
accetgetge agacetegge egegaceaeg et
<210> 320
<211> 769
<212> DNA
<213> Homo sapiens
<400> 320
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tocaactcac cagtgagaga tgagactgcc cagtactcag cottoatoto etgggccace 120
tggagggcgt ctttctccat cagcgcatac tgagcagggg tactcagatc cttcttggaa 180
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gccccttacc ttgagctcct ctatagtagg ttgatgcaat gcatttgaac ctctcctgcc 660
cagcggtatc ccaactggaa ggaaggaaga gtgaagcaca ggtatgtatc ttggggggtg 720
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<210> 321
<211> 690
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> 633, 666
<223> n = A, T, C or G
<400> 321
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cctactcccc cggaggcaac tgggaggtca acgggaagac aatcatcccc tataagaagg 120
gtgcctggtg ttcgctctgc acagccagtg tctcaggctg cttcaaagcc tgggaccatg 180
cagggggget ctgtgaggte cccaggaate cttgtcgcat gagetgccag aaccatggae 240
gteteaacat cagcacetge caetgeeact gteeceetgg etacaeggge agataetgee 300
aagtgaggtg cagcctgcag tgtgtgcacg gccggttccg ggaggaggag tgctcgtgcg 360
tetgtgacat cggctaeggg ggageceagt gtgccaccaa ggtgcatttt ccettccaca 420
cctgtgacct gaggatcgac ggagactgct tcatggtgtc ttcagaggca gacacctatt 480
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aaagtgcagg acatcctcgc cttctatctg ggccgcctgg agaccaccaa cgaggtgact 600
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teettneget gggecacagg ggagcaccag
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<210> 322
<211> 104
<212> DNA
<213> Homo sapiens
<400> 322
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acgctcacat cacggacatc atggagcagg accaccacct ggtc
<210> 323
<211> 118
<212> DNA
<213> Homo sapiens
<400> 323
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actagtgaat gaagaacgaa cactggaagt agaaatagag cctggggtga gagacgga
<210> 324
<211> 354
<212> DNA
<213> Homo sapiens
<400> 324
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taacggagat gatgccgaaa acgcaaggcc gaagccaaag ccaggggatg gagagtttgt 180
ggaagtcatt tctttaccca agaatgacct gctgcagaga cttgatgctc tggtagctga 240
agaacatete acagtggacg ecagggteta tteetacget etagegetga aacatgcaaa 300
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<210> 325
<211> 642
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
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<222> 1
<223> n = A, T, C or G
<400> 325
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gagaggtctg aaattcaggt tcttagtttg ccagggacag gccctacctt atatttttt 240
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gagttatctg ggtggtctct agccatctgg gcagtgtggt tctgtctaac caaagggcat 360
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cccattcaga ctttgccaga gtcaagccaa ggattgcttt tttgctacag ttttctgcca 600
aatggcctag ttcctgagta cctggaaacc agagagaaag ag
<210> 326
<211> 455
<212> DNA
<213> Homo sapiens
<400> 326
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acgatgatga ggcccattct ggactcttct gcctcaatta tccttcggac agattcctgc 180
atcageegga cageggacte egeetettge ttettetgea geacateggt ggeggegett 240
tecetetget tetecaatte ettetette tgageeetga ggtatggttt gatgateaga 300
cggtgcatgg caaagtagac cactagaggc cccacggtgg catagaacat ggcgctgggc 360
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<210> 327
<211> 321
<212> DNA
<213> Homo sapiens
<400> 327
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aagccaccct cttcccgcag catggtgaac aggaagttca taaggacggc gtgtttgcga 180
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gtcttaagga gggtggtgat g
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<210> 328
<211> 476
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 302, 311
<223> n = A, T, C or G
<400> 328
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cagtgtgcag tctgatgaag tctgggtggg tgtggtctac gggctggcag ctaccatgat 120
ccaagaggta atgcactcct tttcccatct ctccaccatc tgtatcctgg ccmagaaaaa 180
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104

cttcccttca aaccaaccaa aatttccttt caaaggcata acccaaatgc catccttggt 240 coggictaat aaagootooc coattitto cotggiatgo attoccaggo tocctggoot 300 throagggott netgicigtg ggtcatagtt tatciccic cactigcigg gageteetig 360 aaggcaaaga ctctactgcc tccatctatc cagtggaagt ggctcttcag agggtgccaa 420 gttagtatgt atgactgtca teteteceaa cagggeetga ettggsaggg etteca <210> 329 <211> 340 <212> DNA <213> Homo sapiens <400> 329 cgagggagat tgccagcacc ctgatggaga gtgagatgat ggagatcttg tcagtgctag 60 ctaagggtga ccacagccct gtcacaaggg ctgctgcagc ctgcctggac aaagcagtgg 120 aatatgggct tatccaaccc aaccaagatg gagagtgagg gggttgtccc tgggcccaag 180 gctcatgcac acgctaccta ttgtggcacg gagagtaagg acggaagcag ctttggctgg 240 tggtggctgg catgeccaat actettgece atcetegett getgeectag gatgteetet 300 gttctgagtc agcggccacg ttcagtcaca cagccctgct <210> 330 <211> 277 <212> DNA <213> Homo sapiens <400> 330 tgtcaccatc acattggtgc caaataccca gaagacatcg tagatgaaga gtccgcccag 60 caggatgcag ccagtgctga cattgttgag gtgcaggagc tctactccat taagggagaa 120 ggccaggcca aaaaggttgt tggcaatcca gtgcttcctc agcaggtacc agacgccaac 180 gatgctgctc aggcccaggc acaccaggtc cttggtgtca aattcataat tgatgatctc 240 ctccttgttt tcccagaacc ctgtgtgaag agcagac <210> 331 <211> 136 <212> DNA <213> Homo sapiens <400> 331 ttgcttccca cctcctttct ctgtcctctc ctgaggttct gccttacaat ggggacactg 60 atacaaacca cacacacaat gaggatgaaa acagataaca ggtaaaatga cctcacctgc 120 ccgggcggcc gctcga 136 <210> 332 <211> 184 <212> DNA <213> Homo sapiens <400> 332 ttgtgagata aacgcagata ctgcaatgca ttaaaacgct tgaaatactc atcagggatg 60 ttgctgatct tattgttgtc taagtagaga gttagaagag agacagggag accagaaggc 120 agtetggeta tetgattgaa geteaagtea aggtattega gtgatttaag acetttaaaa 180 gcag <210> 333 <211> 384 <212> DNA <213> Homo sapiens <400> 333

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aactgaccaa cgatggggaa ctgatcctga ccatgacggc ggatgacgtt gtgtgcacca 360
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<210> 334
<211> 169
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 2, 165
<223> n = A, T, C or G
<400> 334
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aaaattgaat ttccacttcc tgaccgccgc cagaagagat tgattttctc cactatcact 120
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<210> 335
<211> 185
<212> DNA
<213> Homo sapiens
<400> 335
ccaggtttgc agcccaggct gcacatcagg ggactgcctc gcaatacttc atgctgttgc 60
tgctgactga tggtgctgtg acggatgtgg aagccacacg tgaggctgtg gtgcgtgcct 120
cgaacctgcc catgtcagtg atcattgtgg gtgtgggtgg tgctgacttt gaggccatgg 180
agcag
<210> 336
<211> 358
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 26
<223> n = A, T, C or G
<400> 336
ctgcccetgc cttacggcgg ccaganacac acccaggatg gcattggccc caaacttgga 60
tttgttctca gtcccatcca actccagcat caggttgtcc agtttctctt gctccaccac 120
agagagacct gagctgatga gggctggcgo gatggtggag ttgatgtggt ccactgcctt 180
caggacacct ttgcctaagt aacgctgttt gtctccatcc ctcagctcca gggcctcata 240
gatgcccqta gaggctccac tqqqcactgc aqcccggaaa agacctttgg cagtataqag 300
atccacctcc actgtggggt tcccgcggga gtccaggatc tcccgggccc agatcttc
<210> 337
<211> 271
<212> DNA
<213> Homo sapiens
<220>
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<221> misc_feature
<222> 17
<223> n = A, T, C or G
<400> 337
cacaaagcca ccagconggg aaatcagaat ttacttgatg caactgactt gtaatagcca 60
gaaatcctgc ccagcatggg attcagaacc tggtctgcaa ccaaatccac cgtcaaagtt 120
catacaggat aaaacaaatt caattgcctt ttccacatta atagcatcaa gcttccccaa 180
caaagccaaa gttgccaccg cacaaaaaga gaatcttgtg tcaatttctc cctactttat 240
aaaagtagat ttttcacatc ccatgaagca g
                                                                    271
<210> 338
<211> 326
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 15, 17, 18
<223> n = A, T, C or G
<400> 338
ctgtgctccc gactngnnca tctcaggtac caccgactgc actgggcggg gccctctggg 60
gggaaaggct ccacggggca gggatacatc tcgaggccag tcatcctctg gaggcagccc 120
aatcaggtca aagattttgc ccaactggtc ggcttcagag tttccacaga agagaggctt 180
tegacgaaac atetetgeaa agatacagee aacaeteeac atgteeacag gtgttgeata 240
tgtggactgc agaagaactt cgggagctcg gtaccagagt gtaacaacca cgggtgtaag 300
tgccatctgg tagctgtaga ttctgg
<210> 339
<211> 260
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 47, \overline{5}4, 60, 69, 90, 91, 96, 113, 117, 119, 195
<223> n = A, T, C or G
<400> 339
ttcacctgag gactcatttc gtgccctttg ttgacttcaa gcaaagncct tcanggtctn 60
caaggacgnc acatttccac ttgcgaatgn nctcanggct catcttgaag aanaagnanc 120
ccaagtgctg gatcccagac tcgggggtaa ccttgtgggt aagagctcat ccagtttatg 180
ctttaggacg tccanctact cgggggagct ggaagcctgc gtggatgcgg ccctgctgga 240
cctcggccgc gaccacgcta
<210> 340
<211> 220
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 15, 18
<223> n = A, T, C or G
<400> 340
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atcagggcag gtgcactgat aggagccagg caagttatgg cagtcctggc tggggcgaca 180
gtcgtgcagg gcctgggcac actcgtccac atccacacag
<210> 341
<211> 384
<212> DNA
<213> Homo sapiens
<400> 341
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ggcgtcacca gtggcccgtc tgcctcagga actcctccga gtgagggagg agggggctcc 180
tttcccagga tcaaggccac agggaggaag attgcacggg cactgttctg aggaggaagc 240
cccgttggct tacagaagtc atggtgttca taccagatgt gggtagccat cctgaatggt 300
ggcaattata tcacattgag acagaaattc agaaagggag ccagccaccc tggggcagtg 360
aagtgccact ggtttaccag acag
                                                                   384
<210> 342
<211> 245
<212> DNA
<213> Homo sapiens
<400> 342
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tgtaaccaac aagaatgacc ccaagtccat caactctcga gtcttcattg gaaacctcaa 120
cacagetetg qtqaaqaaat caqatqtqqa qaccatette tetaaqtatq qeeqtqtqqc 180
eggetgttet gtgcacaagg getatgeett tgttcagtae tecaatgage gecatgeeg 240
ggcag
<210> 343
<211> 611
<212> DNA
<213> Homo sapiens
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tttcctgcca gtgtcagaaa atcctattta tgaatcctgt cggtattcct tggtatctga 180
aaaaaatacc aaatagtacc atacatgagt tatttctaag tttgaaaaat aaaaagaaat 240
tgcatcacac taattacaaa atacaagttc tggaaaaaat atttttcttc attttaaaac 300
tttttttaac taataatggc tttgaaagaa gaggcttaat ttgggggtgg taactaaaat 360
caaaagaaat gattgacttg agggtctctg tttggtaaga atacatcatt agcttaaata 420
agcagcagaa ggttagtttt aattatgtag cttctgttaa tattaagtgt tttttgtctg 480
ttttacctca atttgaacag ataagtttgc ctgcatgctg gacatgcctc agaaccatga 540
atagcccgta ctagatcttg ggaacatgga tcttagagtc ctttggaata agttcttata 600
taaatacccc c
<210> 344
<211> 311
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 1, 275, 284, 296, 297, 300
<223> n = A, T, C or G
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<400> 344
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aacctgactg caaagtggga agaattacca caactgaaga ctttaaacat ctggctcgca 180
agetgactea eggtgttatg aataaggage tgaagtactg taagaateet gaggacetgg 240
agtgcaatga gaatgtgaaa cacaaaacca aggantacat taanaagtac atgcannaan 300
tttggggctt g
<210> 345
<211> 201
<212> DNA
<213> Homo sapiens
<400> 345
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aatgtcacca tgagtgtgga tgctgagtgt gtgcccatgg tcagggacct tctcaggtac 120
ttctactccc gaaggattga catcaccctg tcgtcagtca agtgcttcca caagctggcc 180
tctgcctatg gggccaggca g
<210> 346
<211> 370
<212> DNA
<213> Homo sapiens
<400> 346
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tctcttcaga atgttctgga gcagcagttt gaggcgggtg atgcgttgga agggcagaat 120
cagaaaggac ttgagggaaa ggcgctggca gacggggtcg ctctccagct tctccaagac 180
ctcccggaaa ttgctgttgc tattcatcag gctctggaag gtgcgttcct gataggtctg 240
gttggtgaca taaggcaggt agacccggcg gaagtctggg gcgtggttca ggactacqtc 300
acatacttgg aaggagaaga tattgttctc aaagttctct tccaggtctg aaaggaacgt 360
ggcgctgacg
<210> 347
<211> 416
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 416
<223> n = A, T, C or G
<400> 347
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ccccatttga acaagcaaag aaggtgataa ccatgtttgt acagcgacag gtgtttgctg 120
agaacaagga tgagattgct ttagtcctgt ttggtacaga tggcactgac aatccccttt 180
ctggtgggga tcagtatcag aacatcacag tgcacagaca tctgatgcta ccagattttg 240
atttgctgga ggacattgaa agcaaaatcc aaccaggttc tcaacaggct gacttcctgg 300
atgcactaat cgtgagcatg gatgtgattc aacatgaaac aataggaaag aagtttggag 360
aagaggcata ttgaaatatt cactgacctc aagcagcccg attcagcaaa agtcan
<210> 348
<211> 351
<212> DNA
<213> Homo sapiens
<400> 348
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qtacaqqaqa qqatqqcaqq tqcaqaqcqq qcactqaqct ctqcaqqtqa aaqqqctcqq 60
caqttqqatq ctctcctqqa qqctctqaaa ttqaaacqqq caqqaaataq tctqqcaqcc 120
tctacagcag aagaaacggc aggcaqtqcc cagggacgag caggagacag atgccttcct 180
cttgtctcaa ctgcaaaqag gcgttccttc ctctttcact aatcctcctc agcacagacc 240
ctttacgggt gtcaggctgg gggacagtaa ggtctttccc ttcccacaag gccatatctc 300
aggctgtctc agtgggggga aaccttggac aatacccggg ctttcttggg c
<210> 349
<211> 207
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 1
<223> n = A, T, C or G
<400> 349
ncegggacat etecaceete aacagtggca agaagageet ggagaetgaa eacaaggeet 60
tgaccagtga gattgcactg ctgcagtcca ggctgaagac agagggctct gatctgtgcg 120
acagagtgag cgaaatgcag aagctggatg cacaggtcaa ggagctggtg ctgaagtcgg 180
cggtggaggc tgagcgcctg gtggctg
<210> 350
<211> 323
<212> DNA
<213> Homo sapiens
<400> 350
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ggggccagca ccatccgtct acttacctcc cttcgggcca agcacaccca ggagaactgt 120
gagacctggg gtgtaaatgg tgagacgggt actttggtgg acatgaagga actgggcata 180
tgggagccat tggctgtgaa gctgcagact tataagacag cagtggagac ggcagttctg 240
ctactgcgaa ttgatgacat cgtttcaggc cacgaaaaga aaggcgatga ccagagccgg 300
caaggegggg cteetgatge tgg
<210> 351
<211> 353
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 12, 25, 39, 42
<223> n = A, T, C or G
<400> 351
egeogeatee entggteeet teeanteeet ttteetttnt engggaaegt gtatgeggtt 60
tgtttttgtt ttgtagggtt tttttccttc tccacctctc cctgtctctt ttgctccatg 120
ttgtccgttt ctgtggggtt aggtttatgt ttttaatcat ctgaggtcac gtctatttcc 180
teeggacteg cetgettggt ggegattete caceggttaa tatggtgegt eeettttte 240
ttttgttgcg aatctgagcc ttcttcctcc agcttctgcc ttttgaactt tgttcttcgg 300
ttctgaaacc atacttttac ctgagtttcc gtgaggctga ggctgtgtgc caa
<210> 352
<211> 467
<212> DNA
<213> Homo sapiens
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aatttgagca gaacctgtct gagaaactct ctgaacaaga attacaattt cgtcgtctca 120
gtcaagagca agttgacaac tttactctgg atataaatac tgcctatgcc agactcagag 180
gaatcgaaca ggctgttcag agccatgcag ttgctgaaga ggaagccaga aaagcccacc 240
aactetgget tteagtggag geattaaagt acageatgaa gaceteatet geagaaacae 300
ctactatece getgggtagt geagttgagg ceateaaage caactgttet gataatgaat 360
tcacccaagc tttaaccgca gctatccctc cagagtccct gacccgtggg gtgtacagtg 420
aagagaccct tagagcccgt ttctatgctg ttcaaaaact ggcccga
<210> 353
<211> 350
<212> DNA
<213> Homo sapiens
<400> 353
etgetgeage caeagtagtt ceteceatgg tgggtggece teetggteet getggeecag 60
gaaatctgtc cccaccagga acagccctg gaaaacggcc ccgtcctcta ccaccttgtg 120
gaaatgctgc acgggaactg cctcctggag gaccagcttt accttcccca gacatttgtc 180
ctgattgtgt agttttcctg gactgcattt caaattgact caggaactgt ttattgcatg 240
gagttacaac aggattetga ccatgaagtt etettttagg taacagatee attaactttt 300
ttgaagatgc ttcagatcca acaccaacaa gggcaaaccc ctttgactgg
<210> 354
<211> 351
<212> DNA
<213> Homo sapiens
<400> 354
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ttttaggttt tttgcttttc taatcaccaa ttcttatata caatgtatat tttagactcg 120
agcagatgat catcttcatc ttaagtcatt ccttttgact gagtatggca ggattagagg 180
gaatggcagt atagatcaat gtctttttct gtaaagtata ggaaaaacca gagaggaaaa 240
aaagagetga caattggaag gtagtagaaa attgaegata atttettett aacaaataat 300
agttgtatat acaaggaggc tagtcaacca gattttattt gttgagggcg a
<210> 355
<211> 308
<212> DNA
<213> Homo sapiens
<400> 355
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ataaaaataa gaaattaagg gttaacatca atgtgccaat gaaaaccgaa cagaagcagg 180
aacaagaaac cacacaaa aacatcgagg aagaccgcaa actactgatt caggcggcca 240
tegtgagaat catgaagatg aggaaggtte tgaaacacca geagttaett ggegaggtee 300
tcactcag
<210> 356
<211> 207
<212> DNA
<213> Homo sapiens
<400> 356
ctgtcccaag tgctcccaga aggcaggatt ctgaagacca ctccagcgat atgttcaact 60
atgaagaata ctgcaccgcc aacgcagtca ctgggccttg ccgtgcatcc ttcccacqct 120
```

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ggtactttga cgtggagagg aactcctgca ataacttcat ctatggaggc tgccggggca 180
ataagaacag ctaccgctct gaggagg
<210> 357
<211> 188
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 25, 29
<223> n = A, T, C or G
<400> 357
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gtgcggccca cgccagcact gcagtgcacc gtgataggcc catcctgtcc aaactgctcc 120
ttggtcttat gcacctgccc gatgaagtca atgaatccct cgcctgtctt gggcacgccc 180
tgctctgg
<210> 358
<211> 291
<212> DNA
<213> Homo sapiens
<400> 358
ctgggagcat cggcaagcta ctgccttaaa atccgatctc cccgagtgca caatttctgt 60
cccttttaag ggttcacaac actaaagatt tcacatgaaa gggttgtgat tgatttgagc 120
aggcaggcgg tacgtgacag gggctgcatg caccggtggt cagagagaaa cagaacaggg 180
cagggaattt cacaatgttc ttctatacaa tggctggaat ctatgaataa catcagtttc 240
taagttatgg gttgattttt aactactggg tttaggccag gcaggcccag g
<210> 359
<211> 117
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 79, \overline{9}8, 100
<223> n = A, T, C or G
<400> 359
gccaccacac tccaqcctgg qcaatacagc aagactgtct caaaaaaaaaa aaaaaaaaa 60
cccaaaaaaa ctcaaaaang taatgaatga tacccaangn gccttttcta gaaaaag
<210> 360
<211> 394
<212> DNA
<213> Homo sapiens
<400> 360
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tegtggttee agtetggttg cagaatetge acatttgeea agaaatttte cetgtttgga 120
aagtttgccc cagctttccc gggcacacca ccttttgtcc caagtgtctg ccggtcgacc 180
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tcagaggtca cccgtgattc tgcctgcacc ttatcattga tctgcagtga tttctgcaaa 360
tcaagagaaa ctctgcaggg cactcccctg tttc
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<210> 361
<211> 394
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 28, 31
<223> n = A, T, C or G
<400> 361
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ggccgcgacc acgctaagcc gaattccagc acactggcgg ccgttactag tggatccgag 360
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<210> 362
<211> 268
<212> DNA
<213> Homo sapiens
<400> 362
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caaacttcaa tggttatgcg gggatgtt
<210> 363
<211> 323
<212> DNA
<213> Homo sapiens
<400> 363
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gacagacact ggcaacattg cggacaccct ccaggaagcg agaatgcaga gtttcctctg 180
tgatatcaag cacttcaggg ttgtagatgc tgccattgtc gaacacctgc tggatgacca 240
geccaaagga gaaggggag atgttgagca tgttcagcag cgtggettcg ctggetecca 300
ctttgtctcc agtcttgatc aga
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<210> 364
<211> 393
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 29
<223> n = A, T, C or G
<400> 364
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acactgtccc ttgcaaggtg acaggccgct gcggctctgt gctggtacgc ctcatcactg 120
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cacccagggg cactggcatc gtctccgcac ctgtgcctaa gaagctgctc atgatggctg 180
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aggecacett tgatgecatt tetaagacet acagetacet gacecegae etetggaagg 300
agactgtatt caccaagtct ccctatcagg agttcactga ccacctcgtc aagacccaca 360
ccagagtete egtgeagegg acteaggete eag
<210> 365
<211> 371
<212> DNA
<213> Homo sapiens
<400> 365
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aggagtteet etecaegtea aagtaeeage gtgggaagga tgeaeggeaa ggeeeagtga 120
ctgcgttggc ggtgcagtat tcttcatagt tgaacatatc gctggagtgg tcttcagaat 180
cetgcettet gggagcactt gggacagagg aatcegetge atteetgetg gtggaceteg 240
gccgcgacca cgctaagccg aattccagca cactggcggc cgttactagt ggatccgagc 300
teggtaceaa gettggegta ateatggtea tagetgttte etgtgtgaaa ttgttateeg 360
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<210> 366
<211> 393
<212> DNA
<213> Homo sapiens
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tggcaaccct tttttctgct gtcagctgga qaqaqatqac taccctqaga atctcatcaa 180
agttcctgcc agtggtagct gggtagagga tagacagctt cagcttctta tcaggaccaa 240
aaacaaacac cacacgagct gccacaggca tgcccttttc atccttctct gctggatcca 300
gcatgcccaa caggatggca agctcccgat tcctatcatc gatgatggga aaaggtaact 360
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<210> 367
<211> 327
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 34, 54, 55
<223> n = A, T, C or G
<400> 367
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gcagaacgat gcgggcattg tccacagtat ttgcgaagat ctgagccctc aggtcctcga 120
tgatcttgaa gtaatggctc cagtctctga cctggggtcc cttcttctcc aagtgctccc 180
ggattttgct ctccagcctc cggttctcgg tctccaggct cctcactctg tccaggtaaq 240
aggecaggeg gtegtteagg ctttgeatgg teteettete gttetggatg ceteecatte 300
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<210> 368
<211> 306
<212> DNA
<213> Homo sapiens
<220>
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<211> 392

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<213> Homo sapiens
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119

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tggagcaagt ctttctagat aagaccetga atgcctcatt ccattggctg ggctccacct 1020
accagttggt ggacatccat gtgacagaaa tggagtcatc agtttatcaa ccaacaagca 1080
getecageae ecageaette tacetgaatt teaceateae caacetacea tatteceagg 1140
acaaagccca gccaggcacc accaattacc agaggaacaa aaggaatatt gaggatgcgc 1200
tcaaccaact cttccgaaac agcagcatca agagttattt ttctgactgt caagtttcaa 1260
cattcaggtc tgtccccaac aggcaccaca ccggggtgga ctccctgtgt aacttctcgc 1320
cactggctcg gagagtagac agagttgcca tctatgagga atttctgcgg atgacccgga 1380
atggtaccca gctgcagaac ttcaccctgg acaggagcag tgtccttgtg gatgggtatt 1440
ttcccaacag aaatgagccc ttaactggga attctgacct tcccttctgg gctgtcatcc 1500
tcatcggctt ggcaggactc ctgggactca tcacatgcct gatctqcqqt qtcctqqtqa 1560
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accagtcaca cctagacctg gaggatctgc aatgactgga acttgccggt gcctggggtg 1680
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<210> 388 <211> 772

121

<212> PRT <213> Homo sapiens

420

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122

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Leu Gly Pro Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr
            440
Asn Glu Pro Gly Pro Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr
                   455
Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His
      470
                                475
Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser
            485
                  490
Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu Gly Val
                        505 510
Leu Glm His Leu Leu Arg Pro Leu Phe Glm Lys Ser Ser Met Gly Pro
515 520
                            525
Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly
             535 540
Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp Pro Val
545 550
                    555 560
Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu
             565
                   570 575
Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser
                          585
Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu
                      600
Tyr Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp
                   615
Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys
             630
                    635
Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe
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            645
Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys
                          665
Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe
                      680
Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr
                  695
                                  700
Gln Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln
               710
                                715
Pro Thr Ser Ser Ser Ser Thr Gln His Phe Tyr Leu Asn Phe Thr Ile
            725
                       730
Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn
        740
                          745
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Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Ala Pro His Arg Gly
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Gly Leu Pro Val
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<210> 389

<211> 833

<212> PRT

<213> Homo sapiens

<400> 389

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 25
 30

 Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu Gln

Leu	Tyr 50	Trp	Glu	Leu	Ser	Gln 55	Leu	Thr	His	Asn	Ile 60	Thr	Glu	Leu	Gly
Pro 65	Tyr	Ala	Leu	Asp	Asn 70	Asp	Ser	Leu	Phe	Val 75	Asn	Gly	Phe	Thr	His 80
Arg	Ser	Ser	Val	Ser 85	Thr	Thr	Ser	Thr	Pro 90	Gly	Thr	Pro	Thr	Val 95	Tyr
Leu	Gly	Ala	Ser 100	Lys	Thr	Pro	Ala	Ser 105	Ile	Phe	Gly	Pro	Ser 110	Ala	Ala
Ser	His	Leu 115	Leu	Ile	Leu	Phe	Thr 120	Leu	Asn	Phe	Thr	Ile 125	Thr	Asn	Leu
Arg	Tyr 130	Glu	Glu	Asn	Met	Trp 135	Pro	Gly	Ser	Arg	Lys 140	Phe	Asn	Thr	Thr
Glu 145	Arg	Val	Leu	Gln	Gly 150	Leu	Leu	Arg	Pro	Leu 155	Phe	Lys	Asn	Thr	Ser 160
Val	Gly	Pro	Leu	Tyr 165	Ser	Gly	Cys	Arg	Leu 170	Thr	Leu	Leu	Arg	Pro 175	Glu
Lys	Asp	Gly	Glu 180	Ala	Thr	Gly	Val	Asp 185	Ala	Ile	Cys	Thr	His 190	Arg	Pro
Asp	Pro	Thr 195	Gly	Pro	Gly	Leu	Asp 200	Arg	Glu	Gln	Leu	Tyr 205	Leu	Glu	Leu
	Gln 210					215					220				
225				-	230		_			235	_				240
	Thr			245					250					255	
	Ile		260					265					270		
	Lys	275				_	280			_		285			
	Phe 290					295					300				
305					310	_		_		315					320
Leu	Cys	Thr	Tyr	Leu 325	Gln	Pro	Leu	Ser	Gly 330	Pro	Gly	Leu	Pro	Ile 335	Lys
	Val		340					345					350		
	Pro	355			_	_	360					365	_	-	
	Pro 370					375					380				
385					390					395					400
	Thr			405					410					415	
	Met		420					425					430		
	His	435					440		_			445			
	Leu 450	_				455					460			_	
	Thr	Gly	Val	Asp		Thr	Cys	Thr	Tyr	His 475	Pro	Asp	Pro	Val	
465 Pro	Gly	Leu	Asp	Ile 485	470 Gln	Gln	Leu	Tyr	Trp 490		Leu	Ser	Gln	Leu 495	480 Thr
His	Gly	Val	Thr 500		Leu	Gly	Phe	Tyr 505		Leu ·	Asp	Arg	Asp 510		Leu

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Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr 520 525 Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro 535 Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val 550 555 560 Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys 565 570 Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys Ala 580 585 Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu 595 600 Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln 610 615 620 Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro 630 635 Thr Ser Ser Ser Ser Thr Gln His Phe Tyr Leu Asn Phe Thr Ile Thr 645 650 Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg 675 680 685 Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe 690 695 700 Arg Ser Val Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys Asn 705 710 715 Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu 730 Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu 745 Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Phe Pro Asn Arg Asn Glu 755 . 760 765 Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu Ile 775 780 Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val 785 790 795 800 Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln 805 810 Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln

<210> 390

<211> 438

<212> PRT

<213> Homo sapiens

<400> 390

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Pro Asp Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu
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             85
Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu
                         105
Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser
                       120
Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu
           135
Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp
    150 155 160
Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp
            165 170 175
Thr Phe Arg Phe Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu
                        185 190
Val Thr Val Lys Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val
       195
                       200 205
Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu
                   215
                                      220
Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu Met Glu Ser
225
                 230
                                   235
Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser Thr Gln His Phe Tyr Leu
              245 250 255
Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro
                           265
          260
Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Leu
                        280
                                         285
Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys
                    295
Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His Thr Gly Val
                310
                                  315
Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val
             325
                              330
Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu
                           345
Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Phe
                        360
Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp
                    375
                                      380
Ala Val Ile Leu Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys
                 390
                                   395
Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly
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                               410
Glu Tyr Asn Val Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu
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Asp Leu Glu Asp Leu Gln
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<210> 391

<211> 2627

<212> DNA

<213> Homo sapiens

<400> 391

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126

tagcatcatc attattctgg ctggagcaat tgcactcatc attggctttg gtatttcagg 180 gagacactcc atcacagtca ctactgtcgc ctcagctggg aacattgggg aggatggaat 240 cctgagctgc acttttgaac ctgacatcaa actttctgat atcgtgatac aatggctgaa 300 ggaaggtgtt ttaggcttgg tccatqagtt caaaqaaggc aaagatqagc tgtcggagca 360 ggatgaaatg ttcagaggcc ggacaqcagt qtttgctgat caaqtgatag ttggcaatgc 420 ctctttgcgg ctgaaaaacg tqcaactcac agatqctggc acctacaaat qttatatcat 480 cacttctaaa ggcaagggga atgctaacct tgagtataaa actggagcct tcaqcatgcc 540 ggaagtgaat gtggactata atgccagctc agagaccttg cggtgtgagg ctccccgatg 600 gttcccccag cccacagtgg tctgggcatc ccaagttgac cagggagcca acttctcgga 660 agtctccaat accagctttg agctgaactc tgagaatgtg accatgaagg ttgtgtctgt 720 gctctacaat gttacgatca acaacacata ctcctgtatg attgaaaatg acattgccaa 780 agcaacaggg gatatcaaag tgacagaatc ggagatcaaa aggcggagtc acctacagct 840 gctaaactca aaggettete tgtgtgtete ttetttettt gccateaget gggcaettet 900 gcctctcagc ccttacctga tgctaaaata atgtgccttg gccacaaaaa agcatgcaaa 960 gtcattgtta caacagggat ctacagaact atttcaccac cagatatgac ctagttttat 1020 atttctggga ggaaatgaat tcatatctag aagtctggag tgagcaaaca agagcaagaa 1080 acaaaaagaa gccaaaagca gaaggctcca atatgaacaa gataaatcta tcttcaaaga 1140 catattagaa gttgggaaaa taattcatgt gaactagaca agtgtgttaa gagtgataag 1200 taaaatgcac gtggagacaa gtgcatcccc agatetcagg gacetecece tgeetgteac 1260 ctggggagtg agaggacagg atagtgcatg ttctttgtct ctgaattttt agttatatgt 1320 gctgtaatgt tgctctgagg aagcccctgg aaagtctatc ccaacatatc cacatcttat 1380 attocacaaa ttaagotgta gtatgtacco taagacgotg ctaattgact gocacttogc 1440 aactcagggg cggctgcatt ttagtaatgg gtcaaatgat tcacttttta tgatgcttcc 1500 aaaggtgeet tggettetet teesaactga caaatgeeaa agttgagaaa aatgateata 1560 attitageat aaacagagea gteggegaca cegattitat aaataaactg ageacettet 1620 ttttaaacaa acaaatgcgg gtttatttct cagatgatgt tcatccgtga atggtccagg 1680 gaaggacctt tcaccttgac tatatggcat tatgtcatca caagctctga ggcttctcct 1740 ttccatcctg cgtggacagc taagacctca gttttcaata gcatctagag cagtgggact 1800 cagctggggt gatttcgccc cccatctccg ggggaatgtc tgaagacaat tttggttacc 1860 tcaatgaggg agtggaggag gatacagtgc tactaccaac tagtggataa aggccaggga 1920 tgctgctcaa cctcctacca tgtacaggac gtctccccat tacaactacc caatccgaag 1980 tgtcaactgt gtcaggacta agaaaccctg gttttgagta gaaaagggcc tggaaagagg 2040 ggagccaaca aatctgtctg cttcctcaca ttagtcattg gcaaataagc attctgtctc 2100 tttggctgct gcctcagcac agagagccag aactctatcg ggcaccagga taacatctct 2160 cagtgaacag agttgacaag gcctatggga aatgcctgat gggattatct tcagcttgtt 2220 gagettetaa gtttettee etteatteta eeetgeaage eaagttetgt aagagaaatg 2280 cotgagttot agetcaggtt ttettactot gaatttagat etccagacce tteetggeca 2340 caattcaaat taaggcaaca aacatatacc ttccatgaag cacacacaga cttttgaaag 2400 caaggacaat gactgcttga attgaggcct tgaggaatga agctttgaag gaaaagaata 2460 ctttgtttcc agccccttc ccacactctt catgtgttaa ccactgcctt cctggacctt 2520 ggagccacgg tgactgtatt acatgttgtt atagaaaact gattttagag ttctgatcgt 2580 tcaagagaat gattaaatat acatttccta caccaaaaaa aaaaaaa 2627

<210> 392

<211> 309

<212> PRT

<213> Homo sapiens

<400> 392

127

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<210> 393

<211> 282

<212> PRT

<213> Homo sapiens

<400> 393

Met Ala Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile 10 Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile Ser 25 Gly Arg His Ser Ile Thr Val Thr Thr Val Ala Ser Ala Gly Asn Ile 40 Gly Glu Asp Gly Ile Leu Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu 55 Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met 90 Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn 105 Ala Ser Leu Arg Leu Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr 120 Lys Cys Tyr Ile Ile Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu 135 Tyr Lys Thr Gly Ala Phe Ser Met Pro Glu Val Asn Val Asp Tyr Asn

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150
                                 155
Ala Ser Ser Glu Thr Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln
           165 170
 Pro Thr Val Val Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser
                          185
 Glu Val Ser Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met
      195 200
 Lys Val Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser
 210 215 220
Cys Met Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val 225 230 235 240
Thr Glu Ser Glu Ile Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser
            245 250 255
Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu
   260 265 270
Leu Pro Leu Ser Pro Tyr Leu Met Leu Lys
<210> 394
<211> 20
<212> PRT
<213> Homo sapiens
<400> 394
Met Ala Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile
1 5
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Ile Ile Leu Ala
<210> 395
<211> 20
<212> PRT
<213> Homo sapiens
<400> 395
 Ile Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile
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 Ser Gly Arg His
<210> 396
<211> 20
 <212> PRT
<213> Homo sapiens
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Asn Ile Gly Glu
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<210> 397
<211> 20
<212> PRT
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<213> Homo sapiens
<400> 397
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1 5
Ile Lys Leu Ser
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<210> 398
<211> 20
<212> PRT
<213> Homo sapiens
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Asp Ile Lys Leu Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val
1 5
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Leu Gly Leu Val
          20
<210> 399
<211> 20
<212> PRT
<213> Homo sapiens
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Val Leu Gly Leu Val His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser
1 5
Glu Gln Asp Glu
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Gln Val Ile Val
          20
<210> 401
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1 5
Leu Thr Asp Ala
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<210> 402 .

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<211> 21
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Lys Gly Lys Gly Asn
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<210> 403
<211> 20
<212> PRT
<213> Homo sapiens
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Met Pro Glu Val
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<211> 20
<212> PRT
<213> Homo sapiens
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Arg Cys Glu Ala
<210> 405
<211> 20
<212> PRT
<213> Homo sapiens
<400> 405
Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln Pro Thr Val Val Trp
1 5
Ala Ser Gln Val
<210> 406
<211> 20
<212> PRT
<213> Homo sapiens
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Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser Glu Val Ser Asn
1
Thr Ser Phe Glu
           20
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<210> 407
<211> 20
<212> PRT
<213> Homo sapiens
<400> 407
Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met Lys Val Val
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1 . 5
Ser Val Leu Tyr
. 20
<210> 408
<211> 20
<212> PRT
<213> Homo sapiens
<400> 408
Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser Cys Met
1 5
                                             15
                              10
Ile Glu Asn Asp
<210> 409
<211> 20
<212> PRT
<213> Homo sapiens
<400> 409
Met 'Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val Thr
1 5
Glu Ser Glu Ile
         20
<210> 410
<211> 20
<212> PRT
<213> Homo sapiens
<400> 410
Thr Glu Ser Glu Ile Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser
1 5
                    10
Lys Ala Ser Leu
          20
<210> 411
<211> 20
<212> PRT
<213> Homo sapiens
<400> 411
Ser Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala
1 5
                               10
                                                15
Leu Leu Pro Leu
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132

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20

<210> 412 <211> 20 <212> PRT <213> Homo sapiens <400> 412 Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu Leu Pro Leu Ser Pro Tyr 1 5 Leu Met Leu Lys 20 <210> 413 <211> 35 <212> PRT <213> Homo sapiens <400> 413 Ile Ser Gly Arg His Ser Ile Thr Val Thr Thr Val Ala Ser Ala Gly 1 5 10 Asn Ile Gly Glu Asp Gly Ile Leu Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu Ser 35 <210> 414 <211> 35 <212> PRT <213> Homo sapiens <400> 414 Val Leu Gly Leu Val His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser 10 Glu Gln Asp Glu Met Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln 25 Val Ile Val 35 <210> 415 <211> 65 <212> PRT <213> Homo sapiens <400> 415 Lys Gly Lys Gly Asn Ala Asn Leu Glu Tyr Lys Thr Gly Ala Phe Ser 10 5 Met Pro Glu Val Asn Val Asp Tyr Asn Ala Ser Ser Glu Thr Leu Arg 20 25 Cys Glu Ala Pro Arg Trp Phe Pro Gln Pro Thr Val Val Trp Ala Ser 40 45 Gln Val Asp Gln Gly Ala Asn Phe Ser Glu Val Ser Asn Thr Ser Phe 55 Glu

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<212> PRT

<213> Homo sapiens ·

133

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65
<210> 416
<211> 10
<212> PRT
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Glu Leu Gly Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn Gly
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Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser
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Thr Met His Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly Pro
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Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu
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Leu Arg Pro Lys Lys Asp Gly Ala Ala Thr Lys Val Asp Ala Ile Cys
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Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln Leu
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Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro
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Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr Gln Arg
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Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr Pro Thr Val Asp Leu
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Gly Thr Ser Gly Thr Pro Val Ser Lys Pro Gly Pro Ser Ala Ala Ser
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Glu Arg Val Leu Gln Gly Leu Leu Arg Ser Leu Phe Lys Ser Thr Ser
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145

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146

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Asn Leu Val Pro Arg Leu Pro Ala Leu Ser Trp Cys Tyr Ser Leu Ser 35 40 45												
Thr Ser Pro Ser Pro Thr Cys Gly Met Arg Arg Thr Cys Ser Thr Leu 50 55 60												
Ala Pro Gly Ser Ser Thr Pro Arg Arg Gly Ser Phe Arg Ala Trp Ser 65 70 75 80												
Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu 85 90 95												
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Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu												
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His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr Pro Thr Val 165 170 175												

Tyr	Leu	Gly	Ala 180	Ser	Lys	Thr	Pro	Ala 185	Ser	Ile	Phe	Gly	Pro 190	Ser	Ala
Ala	Ser	His 195	Leu	Leu	Ile	Leu	Phe 200	Thr	Leu	Asn	Phe	Thr 205	Ile	Thr	Asn
Leu	Arg 210	Tyr	Glu	Glu	Asn	Met 215	Trp	Pro	Gly	Ser	Arg 220	Lys	Phe	Asn	Thr
Thr 225	Glu	Arg	Val	Leu	Gln 230	Gly	Leu	Leu	Arg	Pro 235	Leu	Phe	Lys	Asn	Thr 240
Ser	Val	Gly	Pro	Leu 245	Tyr	Ser	Gly	Суѕ	Arg 250	Leu	Thr	Leu	Leu	Arg 255	Pro
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	_	275		_		_	280	_	_			285	Tyr		
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				325					330				Thr	335	
			340					345					Gln 350		
		355					360				_	365	Leu		
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		_		405					410	_			Leu	415	
			420					425				_	Ile 430		
		435				_	440	_			_	445	Asn		_
	450					455					460		Pro		
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				485					490				Gln Glu	495	
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545					550					555			Ser		560
				565					570				Arg	575	
			580					585					590 Arg		
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625					630					635			J-11		640

Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe 645 650 Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys 660 665 Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe 680 Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr 695 700 Gln Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln 705 710 715 720 Pro Thr Ser Ser Ser Thr Gln His Phe Tyr Leu Asn Phe Thr Ile 725 730 735 Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn 740 745 Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe 755 760 Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr 770 775 Phe Arg Ser Val Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys 790 795 Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu 805 810 Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr 820 825 Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Phe Pro Asn Arg Asn 835 840 845 Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu 855 860 Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly 870 875 Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val 885 890 Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp 905 Leu Gln

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<211> 1148

<212> PRT

<213> Homo sapiens

<400> 479

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Thr	Thr	Ala 115	Ser	Pro	Leu	Leu	Val 120	Leu	Phe	Thr	Ile	Asn 125	Phe	Thr	Ile
Thr	Asn 130	Leu	Arg	Tyr	Glu	Glu 135	Asn	Met	His	His	Pro 140	Gly	Ser	Arg	Lys
Phe 145	Asn	Thr	Thr	Glu	Arg 150	Val	Leu	Gln	Gly	Leu 155	Leu	Arg	Pro	Val	Phe 160
Lys	Asn	Thr	Ser	Val 165	Gly	Pro	Leu	Tyr	Ser 170	Gly	Суѕ	Arg	Leu	Thr 175	Leu
Leu	Arg	Pro	Lys 180	Lys	Asp	Gly	Ala	Ala 185	Thr	Lys	Val	Asp	Ala 190	Ile	Cys
Thr	Tyr	Arg 195	Pro	Asp	Pro	Lys	Ser 200	Pro	Gly	Leu	Asp	Arg 205	Glu	Gln	Leu
Tyr	Trp 210	Glu	Leu	Ser	Gln	Leu 215	Thr	His	Ser	Ile	Thr 220	Glu	Leu	Gly	Pro
Tyr 225	Thr	Leu	Asp	Arg	Asp 230	Ser	Leu	Tyr	Val	Asn 235	Gly	Phe	Thr	Gln	Arg 240
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Gly	Thr	Ser	Gly 260	Thr	Pro	Val	Ser	Lys 265	Pro	Gly	Pro	Ser	Ala 270	Ala	Ser
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	290		Asn			295					300				
305			Leu		310			-		315					320
			Leu	325					330					335	
		_	Thr 340					345					350		
		355	Ser				360					365			
	370		Thr		•	375					380				_
385			Leu		390					395					400
			Thr	405	_				410	-				415	
			Ser 420			_		425					430		
		435	Leu				440				_	445			
	450		Gly		٠.	455					460	-			
465			Arg		470					475					480
			Arg	485					490					495	
			Asp 500					505				•	510		
		515	Arg				520					525			
	530		Glu			535					540				
545			Phe		550					555					560
vaı	vaı	ser	Glu	565	Pro	rne	Tnr	теп	570°	rne	Inr	тте	Asn	575	ьeu

Arg	Tyr	Met	Ala	Asp	Met	Gly	Gln	Pro	Gly	Ser	Leu	Lys	Phe	Asn	Ile
Thr	azA	Asn	580 Val	Met	Lys	His	Leu	585 Leu	Ser	Pro	Leu	Phe	590 Gln	Ara	Ser
	_	595			_		600					605		_	
Ser	ьеи 610	GIĀ	Ala	Arg	Tyr	615	СТĀ	Cys	Arg	vaı	620	Ala	Leu	Arg	Ser
Val 625	Lys	Asn	Gly	Ala	Glu 630	Thr	Arg	Val	Asp	Leu 635	Leu	Cys	Thr	Tyr	Leu 640
	Pro	Leu	Ser	Gly 645	Pro	Gly	Leu	Pro	Ile 650		Gln	Val	Phe	His 655	
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Asp	Lys	Asp 675		Leu	Tyr	Leu	Asn 680	Gly	Tyr	Asn	Glu	Pro 685		Leu	Asp
Glu	Pro 690	Pro	Thr	Thr	Pro	Lys 695	Pro	Ala	Thr	Thr	Phe 700	Leu	Pro	Pro	Leu
Ser 705	Glu	Ala	Thr	Thr	Ala 710	Met	Gly	Tyr	His	Leu 715	Lys	Thr	Leu	Thr	Leu 720
	Phe	Thr	Ile		Asn	Leu	Gln	Tyr			Asp	Met	Gly	-	
Ser	Ala	Thr	Phe	725 Asn	Ser	Thr	Glu	Gly	730 Val	Leu	Gln	His	Leu	735 Leu	Arg
			740		Ser			745					750		
		755					760				-	765		_	
	770			_	Pro	775	_	•	_		780		_		-
Thr 785	Thr	Суѕ	Thr	Tyr	His 790	Pro	Asp	Pro	Val	Gly 795	Pro	Gly	Leu	Asp	Ile 800
Gln	Gln	Leu	Tyr	Trp 805	Glu	Leu	Ser	Gln	Leu 810	Thr	His	Gly	Val	Thr 815	Gln
Leu	Gly	Phe	Tyr 820	Val	Leu	Asp	Arg	Asp 825	Ser	Leu	Phe	Ile	Asn 830	Gly	Tyr
Ala	Pro	Gln 835	Asn	Leu	Ser	Ile	Arg 840	Gly	Glu	Tyr	Gln	Ile 845	Asn	Phe	His
Ile	Val 850	Asn	Trp	Asn	Leu	Ser 855	Asn	Pro	Asp	Pro	Thr 860	Ser	Ser	Glu	Tyr
Ile 865	Thr	Leu	Leu	Arg	Asp 870	Ile	Gln	Asp	Lys	Val 875	Thr	Thr	Leu	Tyr	Lys 880
Gly	Ser	Gln	Leu	His 885	Asp	Thr	Phe	Arg	Phe 890	Cys	Leu	Val	Thr	Asn 895	
Thr	Met	Asp	Ser 900		Leu	Val	Thr	Val 905		Ala	Leu	Phe	Ser 910		Asn
Leu	Asp	Pro 915		Leu	Val	Glu	Gln 920		Phe	Leu	Asp	Lys 925		Leu	Asn
Ala	Ser 930		His	Trp	Leu	Gly 935		Thr	Tyr	Gln	Leu 940		Asp	Ile	His
Val 945		Glu	Met	Glu	Ser		Val	Tyr	Gln	Pro 955		Ser	Ser	Ser	
	Gln	His	Phe	Tyr 965	950 Pro	Asn	Phe	Thr	Ile 970		Asn	Leu	Pro	Tyr 975	960 Ser
Gln	Asp	Lys			Pro	Gly	Thr	Thr 985		Tyr	Gln	Arg			Arg
Asn	Ile		980 Asp	Ala	Leu	Asn	Gln 1000	Leu	Phe	Arg	Asn	Ser		Ile	Lys
Ser	Tyr 1010	-	Ser	Asp	Cys	Gln 101	Val		Thr	Phe	Arg 1020	Ser		Pro	Asn
	His		Thr	Gly	Val	Asp		Leu	Cys		Phe		Pro	Leu	
102)				1030	J				103	ס				1040

161

Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr 1045 1050 1055 Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val 1060 1065 1070 Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn 1075 1080 1085 Ser Asp Leu Pro Phe Trp Ala Val Ile Phe Ile Gly Leu Ala Gly Leu 1090 1095 1100 Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg 1105 1110 1115 1120 Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly 1125 1130 Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln 1140 1145

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<213> Homo sapiens

<400> 480

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<210> 481

<211> 210

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<210> 483 <211> 438 <212> PRT <213> Homo sapiens

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Thr	Glu	Gly 35	Val	Leu	Gln	His	Leu 40	Leu	Arg	Pro	Leu	Phe 45	Gln	Lys	Ser
Ser	Met 50	Gly	Pro	Phe	Tyr	Leu 55	Gly	Cys	Gln	Leu	Ile 60	Ser	Leu	Arg	Pro
Glu 65	Lys	Asp	Gly	Ala	Ala 70	Thr	Gly	Val	Asp	Thr 75	Thr	Cys	Thr	Tyr	His 80
Pro	Asp	Pro	Val	Gly 85	Pro	Gly	Leu	Asp	Ile 90	Gln	Gln	Leu	Tyr	Trp 95	Glu
			100		His	_		105			_		110		
		115			Phe		120	_	-			125			
	130	_			Gln	135					140		_		
145			_		Thr 150				_	155				_	160
				165	Thr				170					175	
			180		Leu			185				_	190		
		195			Leu		200				_	205			
	210				Asp	215					220			-	
225					Leu 230					235					240
				245	Thr				250					255	
			260		Asn			265					270		
		275		-	Gln	_	280	_	-			285	_		
	290				Asn	295					300				
305					Arg 310					315				_	320
				325	Phe				330	-	_		_	335	
			340		Phe			345					350		
		355			Asp		360					365	_	_	
	370				Pro	375					380				
385					Gly 390					395					400
				405	Leu				410					415	
			420		Gln	GIN	cys	425	ĊΤÀ	Tyr	туr	GIN	430	HIS	ьeu
nsp	neu	435	Asp	neu	GIII										

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PCT/US01/22635

WO 02/06317

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<211> 216
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Met Ser Met Val Ser Pro Ile Arg Ala Leu Cys Pro Pro Pro Ala Leu
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Leu Gly Pro Pro Gln Trp Ile Ser Glu Pro Gln Trp Thr Pro Ser Ser
                       40
Leu Ser Ser Pro Thr Ile Met Ala Ala Gly Pro Leu Leu Val Pro Phe
                    55
Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Gly
                                  75
His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly
             85
                              90
Leu Leu Gly Pro Ile Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser
         100 105 110
Gly Cys Arg Leu Thr Ser Leu Arg Ser Lys Lys Asp Gly Ala Ala Thr
     115 120 125
Gly Val Asp Ala Ile Cys Ile His His Leu Asp Pro Lys Ser Pro Gly
   130 . 135
Leu Asn Arg Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly
               150 155 160
Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val
             165
                              170
Asn Gly Phe Thr His Arg Thr Ser Val Pro Thr Thr Ser Thr Pro Gly
       180 185
Thr Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Leu Pro
 195 200 205
Ala Thr Gln Ser Leu Ala Leu Ser
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                       40
Glu Asp Met Arg Arg Thr Gly Ser Arg Lys Phe Asn Thr Met Glu Ser
                 55
                               60
Val Leu Gln Gly Leu Leu Lys Pro Leu Phe Lys Asn Thr Ser Val Gly
                        75
             70
Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Lys Lys Asp
                             90
Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Leu Asp Pro
          100
                           105
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165

Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr Trp Glu Leu Ser Lys 115 120 Leu Thr Asn Asp Ile Glu Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn 135 Ser Leu Tyr Val Asn Gly Phe Thr His Gln Ser Ser Val Ser Thr Thr 150 155 Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Arg Thr Ser Val Asp Ser 165 170 175 Ile Leu Pro Leu Gln Pro His Asn Tyr Gly Cys Trp Pro Ser Pro Gly 185 Thr Ile His Pro Gln Leu His His Gln Pro Ala Val Trp Gly Gly 200 His Gly Ser Pro Trp Leu Gln Glu Val Gln His His Arg Glu Gly Pro 210 215 Ala Gly Ser Ala Trp Ser His Ile Gln Glu His Gln Cys Trp Pro Ser 225 230 235 Val Leu Trp Leu Gln Thr Asp Leu Ser Gln Val Gln Glu Gly Trp Ser 245 250 Ser His Trp Ser Gly Cys His Leu His Pro Ser Ser

<210> 486

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<213> Homo sapiens

<400> 486

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166

Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro 255

Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr 260

Leu Asn Ser His Leu Gln Ser Pro Val Phe Thr Arg Tyr Gly Gln Gly 275

Leu Lys Val His Ser Ile His Arg Gly Gly Ser Phe Ser Asn Trp Ser 290

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167

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<210> 489 <211> 178 <212> PRT

<213> Homo sapiens

<400> 489

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Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp
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              165 170
Pro Phe
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Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu
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gataagaccc tgaatgcctc attccattgg ctgggctcca cctaccagtt ggtggacatc 9900
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aacagcagca tcaagagtta tttttctgac tgtcaagttt caacattcag gtctgtcccc 10140
aacaggcacc acaccggggt ggactccctg tgtaacttct cgccactggc tcggagagta 10200
gacagagttg ccatctatga ggaatttctg cggatgaccc ggaatggtac ccagctgcag 10260
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cccttaactg ggaattctga ccttcccttc tgggctgtca tcytcatcgg cttggcagga 10380
ctcctgggac tcatcacatg cctgatctgc ggtgtcctgg tgaccacccg ccggcggaag 10440
aaggaaggag aatacaacgt ccagcaacag tgcccaggct actaccagtc acacctagac 10500
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<210> 570
<211> 469
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 71,92,93,120,124,168,178,218,230,300,
     321, 350, 387, 412, 414, 415, 422, 423, 451
<223> n = A, T, C or G
<400> 570
gtttcaccca tcggagctct gtgcccacca ccagcactcc tgggacctcc acagtggacc 60
tgggaacetc wgggactcca tcctccctcc cyrgccccac agctgctggc cctctcctgr 120
tgcyattcac cctcaacttc accatcacca acctgeagta tgaggagrac atgcatcrcc 180
ctggctccag gaagttcaac accacggaga gggtcctkca gggtctgcty aggtcccttg 240
ttcaagaaca ccagtgttgg ccctctgtac tctggctgca gactgacctt gctcaggccy 300
gagaaggatg gggcagccac yggagtggat gccatctgca cccaccgccy tgaccccaaa 360
agecetggae tggacagaga geagetrtae tgggagetga geeagetgae emayrgeate 420
amwgagetgg geceetaeae eetggaeagg racagtetet atgteaatg
<210> 571
<211> 130
<212> PRT
<213> Homo sapiens
<220>
<221> variant
<222> 69,107,110
<223> Xaa = Any amino acid
<400> 571
His Pro Gln Leu Glu Gln Gln Pro Gln Ser His Ser Trp Cys His Ser
                                    10
Pro Ser Thr Ser Thr His His Gln Pro Ala Val Arg Gly Gly His Ala
                                25
                                                    30
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190

Ala Pro Gly Ser Arg Lys Phe Asn Ala His Arg Glu Arg Thr Ala Gly 35 40 45

Ser Cys Ser Asn Pro Arg Ser Gly Ile Ala Val Trp Asn Thr Ser Ile 50 60

Gln Ala Ala Asp Xaa Pro His Ser Gly Gln Arg Arg Ile Ala Gln Pro 65 70 75 80

Arg Gln Trp Met Pro Ser Ala His Ile Ala Leu Thr Leu Lys Thr Ser 85 90 95

Asp Trp Thr Glu Ser Asp Cys Thr Gly Ser Xaa Ala Ile Xaa Gln Met 100 105 . 110

Ala Ser Arg Ser Trp Ala Pro Thr Pro Trp Thr Gly Thr Val Ser Met 115 120 125

Ser Met 130

<210> 572

<211> 130

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 1,58,78,92,94

<223> Xaa = Any amino acid

<400> 572

Xaa Ile Pro Ser Ser Asn Ser Ser His Ser Pro Ile His Gly Ala Ile 5 10 15

His Pro Gln Leu Gln Leu Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met
20 25 30

Arg His Leu Val Pro Gly Ser Ser Thr Arg Thr Glu Arg Glu Leu Gln
35 40 45

Gly Arg Ala Gln Thr Leu Asp Gln Glu Xaa Gln Ser Gly Ile Pro Leu
50 60

Phe Arg Leu Gln Thr Ser Leu Thr Gln Ala Arg Glu Gly Xaa Leu Ser 65 70 75 80

His Gly Ser Gly Cys His Leu His Thr Ser Pro Xaa Pro Xaa Arg Pro 85 90 95

Arg Thr Gly Gln Arg Ala Thr Val Leu Gly Ala Glu Gln Ser Asp Lys 100 105 110

Trp His Pro Gly Ala Gly Pro Leu His Pro Gly Pro Glu Gln Ser Leu 115 120 125

Cys Gln

191

130

<210> 573

<211> 130

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 1,54

<223> Xaa = Any amino acid

<400> 573

Xaa Ser Pro Ala Arg Thr Ala Ala Thr Val Pro Phe Met Val Pro Phe 5 10 15

Thr Leu Asn Phe Asn Ser Ser Pro Thr Cys Ser Thr Arg Arg Thr Cys
20 25 30

Gly Thr Trp Phe Gln Glu Val Gln Arg Ala Gln Arg Glu Asn Cys Arg 35 40 45

Val Val Leu Lys Pro Xaa Ile Arg Asn Ser Ser Leu Glu Tyr Leu Tyr 50 55 60

Ser Gly Cys Arg Leu Ala Ser Leu Arg Pro Glu Lys Asp Ser Ser Ala 65 70 75 80

Thr Ala Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Glu Asp Leu 85 90 95

Gly Leu Asp Arg Glu Arg Leu Tyr Trp Glu Leu Ser Asn Leu Thr Asn 100 105 110

Gly Ile Gln Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr 115 120 125

Val Asn 130

<210> 574

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 101

<223> Xaa = Any amino acid

<400> 574

Gly Phe Thr His Arg Ser Ser Met Pro Thr Thr Ser Thr Pro Gly Thr

Ser Thr Val Asp Val Gly Thr Ser Gly Thr Pro Ser Ser Ser Pro Ser 20 25 30

Pro Thr Thr Ala Gly Pro Leu Leu Met Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met Arg Arg Thr Gly Ser Arg 50 55 60

Lys Phe Asn Thr Met Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Xaa Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Lys Leu Thr Asn Asp Ile Glu Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 575

<211> 158

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 103

<223> Xaa = Any amino acid

<400> 575

Gly Phe Thr His Gln Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr 5 10 15

Ser Thr Val Asp Leu Arg Thr Ser Val Thr Pro Ser Ser Leu Ser Ser 20 25 30

Pro Thr Ile Met Ala Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn 35 40 45

Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Gly His Pro Gly 50 55 60

Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly 65 70 75 80

Pro Ile Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg \$85\$ 90 \cdot 95

Leu Thr Ser Leu Arg Ser Xaa Lys Asp Gly Ala Ala Thr Gly Val Asp 100 105 110

Ala Ile Cys Ile His His Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg 115 120 125

Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu 130 135 140

Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 576

<211> 122

<212> PRT

<213> Homo sapiens

<400> 576

Ala Ala Gly Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr Ile Thr 5 10 15

Asn Leu Lys Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg Lys Phe 20 25 30

Asn Thr Thr Glu Arg Val Leu Gln Thr Leu Arg Gly Pro Met Phe Lys 35 40

Asn Thr Ser Gly Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu 50 60

Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr
65 70 75 80

His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu Tyr
85 90 95

Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu Leu Gly Pro Tyr
100 105 110

Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn

<210> 577

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 11,106,151

<223> Xaa = Any amino acid

<400> 577

Gly Phe Thr His Arg Thr Ser Val Pro Thr Xaa Ser Thr Pro Gly Thr

Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Phe Ser Leu Pro Ser 20 25 30

Pro Ala Thr Ala Gly Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Lys Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg 50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Thr Leu Leu Gly Pro Met 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Ser Glu Lys Asp Gly Ala Xaa Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Xaa Ser Leu Tyr Val Asn 145 150 155

<210> 578

<211> 155

<212> PRT

<213> Homo sapiens

<400> 578

Gly Phe Thr His Trp Ile Pro Val Pro Thr Ser Ser Thr Pro Gly Thr $^{\prime}$ 10 15

Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro 20 25 30

Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile 35 40 45

Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg Lys 50 55 60

Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Met Phe 65 70 75 80

Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu 85 90 95

Leu Arg Pro Glu Lys Asn Gly Ala Ala Thr Gly Met Asp Ala Ile Cys 100 105 110

Ser His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu 115 120 125

Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Lys Glu Leu Gly Pro 130 135 140

Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn 150 <210> 579 <211> 155 <212> PRT <213> Homo sapiens <220> <221> variant <222> 52,138 <223> Xaa = Any amino acid Gly Phe Thr His Trp Ile Pro Val Pro Thr Ser Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Xaa Tyr Glu Glu Asp Met His Cys Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Ser Leu Leu Gly Pro Met Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys 105 Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Xaa Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Ser Asn Ser Leu Tyr Val Asn 150 <210> 580 <211> 156 <212> PRT <213> Homo sapiens <220> <221> variant <222> 23 <223> Xaa = Any amino acid <400> 580 Gly Phe Thr His Gln Thr Ser Ala Pro Asn Thr Ser Thr Pro Gly Thr

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10 Ser Thr Val Asp Leu Gly Xaa Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr Ser Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Met Phe Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asn Gly Ala Ala Thr Gly Met Asp Ala Ile Cys Ser His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Lys Glu Leu Gly 135 Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn <210> 581 <211> 156 <212> PRT <213> Homo sapiens <400> 581 Gly Phe Thr His Arg Ser Ser Val Ala Pro Thr Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr Thr Ala Val Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Arg His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Leu Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Ile Ser Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile 105 Cys Thr His His Leu Asn Pro Gln Ser Pro Gly Leu Asp Arg Glu Gln

197

115 120 125 Leu Tyr Trp Gln Leu Ser Gln Met Thr Asn Gly Ile Lys Glu Leu Gly 130 135 Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 150 <210> 582 <211> 156 <212> PRT <213> Homo sapiens <220> <221> variant <222> 151 <223> Xaa = Any amino acid <400> 582 Gly Phe Thr His Arg Ser Ser Gly Leu Thr Thr Ser Thr Pro Trp Thr Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Pro Val Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg Lys Phe Asn Ala Thr Glu Arg Val Leu Gln Gly Leu Leu Ser Pro Ile Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Met Asp Ala Val Cys Leu Tyr His Pro Asn Pro Lys Arg Pro Gly Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly Pro Tyr Ser Leu Asp Arg Xaa Ser Leu Tyr Val Asn 150 <210> 583

<210> 583 <211> 156 <212> PRT <213> Homo sapiens <220>

<221> variant

198

<222> 109,114,117,128,139 <223> Xaa = Any amino acid

<400> 583

Gly Phe Thr His Gln Asn Ser Val Pro Thr Thr Ser Thr Pro Gly Thr 5 10 15

Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Phe Pro Gly 20 25 30

His Thr Glu Pro Gly Pro Leu Leu Ile Pro Phe Thr Phe Asn Phe Thr 35 40

Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg 50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Thr Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Gln Glu Ala Ala Thr Gly Xaa Asp Thr Ile 100 105 110

Cys Xaa His Arg Xaa Asp Pro Ile Gly Pro Gly Leu Asp Arg Glu Xaa 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Xaa Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 584

<211> 156

<212> PRT

<213> Homo sapiens

<400> 584

Gly Phe Asn Pro Trp Ser Ser Val Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Ser Thr Val His Leu Ala Thr Ser Gly Thr Pro Ser Ser Leu Pro Gly
20 25 30

His Thr Ala Pro Val Pro Leu Leu Ile Pro Phe Thr Leu Asn Phe Thr 35 \cdot 40 45

Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg 50 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys His Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr Leu Arg Leu Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Arg 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Ser Val Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 585

<211> 156

<212> PRT

<213> Homo sapiens

<400> 585

Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr
5 10 15

Ser Ala Val His Leu Glu Thr Ser Gly Thr Pro Ala Ser Leu Pro Gly 20 25 30

His Thr Ala Pro Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met Arg His Pro Gly Ser Arg 50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Arg Gly Ala Ala Thr Gly Val Asp Thr Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Leu Asn Pro Gly Leu Asp Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Lys Leu Thr Cys Gly Ile Ile Glu Leu Gly 130 135 140

Pro Tyr Leu Leu Asp Arg Gly Ser Leu Tyr Val Asn 145 150 155

<210> 586

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 151,156

<223> Xaa = Any amino acid

<400> 586

Gly Phe Thr His Arg Asn Phe Val Pro Ile Thr Ser Thr Pro Gly Thr 5 10 15

Ser Thr Val His Leu Gly Thr Ser Glu Thr Pro Ser Ser Leu Pro Arg 20 25 30

Pro Ile Val Pro Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Ala Met Arg His Pro Gly Ser Arg
50 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Ile Gly Pro Leu Tyr Ser Ser Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Lys Ala Ala Thr Arg Val Asp Ala Ile 100 105 110

Cys Thr His His Pro Asp Pro Gln Ser Pro Gly Leu Asn Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Xaa Ser Leu Tyr Val Xaa 145 150 155

<210> 587

<211> 156

<212> PRT

<213> Homo sapiens

<400> 587

Gly Phe Thr His Trp Ser Pro Ile Pro Thr Thr Ser Thr Pro Gly Thr 10 15

Ser Ile Val Asn Leu Gly Thr Ser Gly Ile Pro Pro Ser Leu Pro Glu 20 25 30

Thr Thr Ala Thr Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Lys Phe Asn Ile Thr Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Val Ala Thr Arg Val Asp Ala Ile 100 105 110

Cys Thr His Arg Pro Asp Pro Lys Ile Pro Gly Leu Asp Arg Gln Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 588

<211> 156

<212> PRT

<213> Homo sapiens

<400> 588

Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Phe Thr Val Gln Pro Glu Thr Ser Glu Thr Pro Ser Ser Leu Pro Gly 20 25 30

Pro Thr Ala Thr Gly Pro Val Leu Leu Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Ile Asn Leu Gln Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg 50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Met Pro Leu
65 70 75 80

Phe Lys Asn Thr Ser Val Ser Ser Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Arg Val Asp Ala Val
100 105 110

Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Arg 115 120 125

Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn 145 150 155

<210> 589

<211> 156

<212> PRT

<213> Homo sapiens

<400> 589

Gly Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr

202

5 10 15 Ser Thr Met His Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly 25 Pro Thr Thr Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met His His Pro Gly Ser Arg 55 Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Lys Lys Asp Gly Ala Ala Thr Lys Val Asp Ala Ile Cys Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly 135 Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn <210> 590 <211> 156 <212> PRT <213> Homo sapiens <220> <221> variant <222> 145 <223> Xaa = Any amino acid <400> 590 Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr Pro Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Val Ser Lys Pro Gly Pro Ser Ala Ala Ser Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr 35 Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Ser Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr

203

Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly 130 135 140

Xaa Tyr Ala Leu Asp Asn Asp Ser Leu Phe Val Asn 145 150 155

<210> 591

<211> 155

<212> PRT

<213> Homo sapiens

<400> 591

Gly Phe Thr His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr 5 10 15

Pro Thr Val Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser Ile Phe Gly 20 25 30

Pro Ser Ala Ala Ser His Leu Leu Ile Leu Phe Thr Leu Asn Phe Thr 35 40

Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Trp Pro Gly Ser Arg Lys 50 55 60

Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe 65 70 75 80

Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu 85 90 95

Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys 100 105 110

Thr His Arg Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu 115 120 125

Tyr Leu Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro 130 135 140

Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 592

<211> 134

<212> PRT

<213> Homo sapiens

<400> 592

Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val Val

204

10 15 Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn 130 <210> 593 <211> 150 <212> PRT <213> Homo sapiens <220> <221> variant <222> 7 <223> Xaa = Any amino acid Gly Tyr Asn Glu Pro Gly Xaa Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp 105

Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser 115 120 125

Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg 130 135 140

Asp Ser Leu Phe Ile Asn 145 150

<210> 594

<211> 318

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 136,248,268

<223> Xaa = Any amino acid

<400> 594

Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn 5 10 15

Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser 20 25 30

Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$

Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr 50 55 60

Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser 65 70 75 80

Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr 85 90 95

Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp 100 105 110

Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser 115 120 125

Ser Ser Thr Gln His Phe Tyr Xaa Asn Phe Thr Ile Thr Asn Leu Pro 130 135 140

Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn 145 150 155 160

Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser 165 170 175

Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val

206

Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro 195 200 205 Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg 215 Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Xaa Pro Asn Arg Asn Glu Pro Leu Thr 250 Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Xaa Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr 280 Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys 295 Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln 310 315 <210> 595 <211> 3451 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> 177, 335, 523, 618, 663, 875, 961, 1001, 1441, 1555, 1560, 1563, 1574, 1585, 2065, 2070, 2683, 2990, 3269, 3381, 3401 <223> Xaa = Any Amino Acid <400> 595 Ile Arg Asn Ser Ser Leu Glu Tyr Leu Tyr Ser Gly Cys Arg Leu Ala 10 Ser Leu Arg Pro Glu Lys Asp Ser Ser Ala Thr Ala Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Glu Asp Leu Gly Leu Asp Arg Glu Arg 40 Leu Tyr Trp Glu Leu Ser Asn Leu Thr Asn Gly Ile Gln Glu Leu Gly 55 Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His 75 70 Arg Ser Ser Met Pro Thr Thr Ser Thr Pro Gly Thr Ser Thr Val Asp 85 90 Val Gly Thr Ser Gly Thr Pro Ser Ser Ser Pro Ser Pro Thr Thr Ala 105 Gly Pro Leu Leu Met Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu 120 125 Gln Tyr Glu Glu Asp Met Arg Arg Thr Gly Ser Arg Lys Phe Asn Thr 135 140

Met Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu Phe Lys Asn Thr

Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro

155

150

207

165 170 175 Xaa Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg 185 180 Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr Trp Glu 200 Leu Ser Lys Leu Thr Asn Asp Ile Glu Glu Leu Gly Pro Tyr Thr Leu 215 220 Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His Gln Ser Ser Val 230 235 240 Ser Thr Thr Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Arg Thr Ser <u>.</u> 245 250 Val Thr Pro Ser Ser Leu Ser Ser Pro Thr Ile Met Ala Ala Gly Pro 260 265 Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr 280 285 Gly Glu Asp Met Gly His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu 295 300 Arg Val Leu Gln Gly Leu Leu Gly Pro Ile Phe Lys Asn Thr Ser Val 310 315 Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Ser Leu Arg Ser Xaa Lys 325 330 Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Ile His His Leu Asp 340 345 Pro Lys Ser Pro Gly Leu Asn Arg Glu Arg Leu Tyr Trp Glu Leu Ser 360 365 Gln Leu Thr Asn Gly Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg 375 380 Asn Ser Leu Tyr Val Asn Ala Ala Gly Pro Leu Leu Val Leu Phe Thr 390 395 Leu Asn Phe Thr Ile Thr Asn Leu Lys Tyr Glu Glu Asp Met His Arg 405 410 Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Thr Leu 420 425 Arg Gly Pro Met Phe Lys Asn Thr Ser Gly Gly Leu Leu Tyr Ser Gly 440 435 445 Cys Arg Leu Thr Leu Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly 450 455 460 Val Asp Ala Ile Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val 470 475 Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile 485 490 495 Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 500 505 510 Gly Phe Thr His Arg Thr Ser Val Pro Thr Xaa Ser Thr Pro Gly Thr 515 520 525 Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Phe Ser Leu Pro Ser 535 540 Pro Ala Thr Ala Gly Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr 555 Ile Thr Asn Leu Lys Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg 565 570 Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Thr Leu Leu Gly Pro Met 580 585 590 Phe Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr 600 605 Leu Leu Arg Ser Glu Lys Asp Gly Ala Xaa Thr Gly Val Asp Ala Ile 615 Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln

625					630					635					640
Leu	Tyr	Trp	Glu	Leu 645	Ser	Gln	Leu	Thr	Asn 650	Gly	Ile	Lys	Glu	Leu 655	Gly
Pro	Tyr	Thr	Leu 660	Asp	Arg	Xaa	Ser	Leu 665	Tyr	Val	Asn	Gly	Phe 670	Thr	His
Trp	Ile	Pro 675	Val	Pro	Thr	Ser	Ser 680	Thr	Pro	Gly	Thr	Ser 685	Thr	Val	Asp
Leu	Gly 690	Ser	Gly	Thr	Pro	Ser 695	Ser	Leu	Pro	Ser	Pro	Thr	Thr	Ala	Gly
Pro 705	Leu	Leu	Val	Pro	Phe 710	Thr	Leu	Asn	Phe	Thr 715	Ile	Thr	Asn	Leu	Gln 720
Tyr	Glu	Glu	Asp	Met 725	His	His	Pro	Gly	Ser 730		ŗЛs	Phe	Asn	Thr 735	
Glu	Arg	Val	Leu 740		Gly	Leu	Leu	Gly 745		Met	Phe	Lys	Asn 750		Ser
Val	Gly	Leu 755	Leu	Tyr	Ser	Gly	Cys 760	Arg	Leu	Thr	Leu	Leu 765		Pro	Glu
Lys	Asn 770	Gly	Ala	Ala	Thr	Gly 775	Met	Asp	Ala	Ile	Cys 780	Ser	His	Arg	Leu
Asp 785	Pro	Lys	Ser	Pro	Gly 790	Leu	Asn	Arg	Glu	Gln 795	Leu	Tyr	Trp	Glu	Leu 800
Ser	Gln	Leu	Thr	His 805	Gly	Ile	Lys	Glu	Leu 810	Gly	Pro	Tyr	Thr	Leu 815	Asp
Arg	His	Ser	Leu 820	Tyr	Val	Asn	Gly	Phe 825	Thr	His	Trp	Ile	Pro 830	Val	Pro
Thr	Ser	Ser 835	Thr	Pro	Gly	Thr	Ser 840	Thr	Val	Asp	Leu	Gly 845	Ser	Gly	Thr
Pro	Ser 850	Ser	Leu	Pro	Ser	Pro 855	Thr	Thr	Ala	Gly	Pro 860	Leu	Leu	Val	Pro
Phe 865	Thr	Leu	Asn	Phe	Thr 870	Ile	Thr	Asn	Leu	Xaa 875	Tyr	Glu	Glu	Asp	Met 880
			_	885	_	Lys			890			_		895	
Ser	Leu	Leu	Gly 900	Pro	Met	Phe	Lys	Asn 905	Thr	Ser	Val	Gly	Pro 910	Leu	Tyr
	_	915	_			Leu	920	_			_	925	_		
	930					Cys 935					940		_		
945					950	Leu				955					960
				965		Pro	_		970	_				975	
			980			Gln		985					990		
		995				Leu	1000)				1005	5		
	1010)				Gly 1015	5				1020)			
1025	5				1030		-			1039	5				1040
				1045	5	Thr			1050)				1055	5
			1060)		Ser		1065	5				1070)	
		1075	5			Glu	1080)				1085	5		_
Ala	Ile	Cys	Ser	His	Arg	Leu	Asp	Pro	Lys	Ser	Pro	Gly	Leu	Asn	Arg

209

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Val Asn Gly Phe	Asn Pro Trp 1605	Ser Ser Val		Thr Ser	Thr Pro 1615
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Phe Thr Ile Thr 1650	Asn Leu His		Asn Met 1660		Pro Gly
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Val His Leu Glu 178	0	1785		1790	כ
Ala Pro Gly Pro 1795		1800		1805	
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Val Ser Glu Glu 2865	2870		2875			2880
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Lys Asn Gly Ala 2930	293	5		2940		
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Arg Val Asp A 3345		3350	_		3355				3360
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214

3410 3415 3420

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<400> 596

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Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg
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Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln
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Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

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- (71) Applicant (for all designated States except US): CORIXA CORPORATION [US/US]; 1124 Columbia Street, Suite 200, Seattle, WA 98104 (US).
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09/884,441	18 June 2001 (18.06.2001)	US

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[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

11729.1 contg

11729-45.21.21.cons1

11729-45.21.21.cons2

11731.lcontig

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as ovarian cancer, are disclosed. Compositions may comprise one or more ovarian carcinoma proteins, immunogenic portions thereof, polynucleotides that encode such portions or antibodies or immune system cells specific for such proteins. Such compositions may be used, for example, for the prevention and treatment of diseases such as ovarian cancer. Methods are further provided for identifying tumor antigens that are secreted from ovarian carcinomas and/or other tumors. Polypeptides and polynucleotides as provided herein may further be used for the diagnosis and monitoring of ovarian cancer.



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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

stional Application No

		PC1/03 01/22035
	G01N33/574 C12Q1/68 C12N15/62 C A61K39/395	12N5/10 C07K16/30 12N5/06 A61K39/00
	o International Patent Classification (IPC) or to both national classification and IPC	
	SEARCHED	
IPC 7	ocumentation searched (classification system followed by classification symbols) CO7K C12N G01N C12Q A61K	
Documental	tion searched other than minimum documentation to the extent that such documen	ts are included in the fields searched
	ata base consulted during the international search (name of data base and, where ternal, WPI Data, PAJ, BIOSIS, MEDLINE	e practical, search terms used)
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	ENTS CONSIDERED TO BE RELEVANT	Delevent to claim Ma
Category °	Citation of document, with indication, where appropriate, of the relevant passage	es Relevant to claim No.
Х	WO 00 36107 A (CORIXA CORP) 22 June 2000 (2000-06-22)	1-3,7, 15, 19-32,35
	SEQ ID N0:311, 312, 385-390 encoding 077 polynucleotides and polypeptides pages 48, 50, 51 claims 1,2,7,8,13-17,21,33,37,39,42,49	/27
Α	SCHUMMER MICHEL ET AL: "Comparative hybridization of an array of 21 500 ovarian cDNAs for the discovery of generoverexpressed in ovarian carcinomas." GENE (AMSTERDAM), vol. 238, no. 2, 1 October 1999 (1999-10-01), pages 375-385, XP002222131 ISSN: 0378-1119 the whole document	1,7,24, 25,32
Furth	ner documents are listed in the continuation of box C. X Pate	ent family members are listed in annex.
"A" documer conside "E" earlier de filling de "L" documer which is citation "O" documer other m" "P" documer later this	ant defining the general state of the art which is not cited to be of particular relevance inwention locument but published on or after the international ate in which may throw doubts on priority claim(s) or is cited to establish the publication date of another or or other special reason (as specified) in the referring to an oral disclosure, use, exhibition or means int published prior to the international filing date but an the priority date claimed in the international search in the actual completion of the international search in the actual completion i	at of particular relevance; the claimed invention be considered novel or cannot be considered to an inventive step when the document is taken alone at of particular relevance; the claimed invention be considered to involve an inventive step when the intermediate to combined with one or more other such docustic combination being obvious to a person skilled
1	1 December 2002	
Name and m	European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk	rouns, G

INTERNATIONAL SEARCH REPORT

Iternational application No. PCT/US 01/22635

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: see FURTHER INFORMATION sheet PCT/ISA/210
Claims Nos.: Claims Nos.: Decause they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: See FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple Inventions in this international application, as follows:
see additional sheet
As all required additional search fees were timely paid by the applicant, this international Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. X No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-3, 7, 15, 19-32, 35 all partially
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

Continuation of Box I.1

Although claims 25 and 32 are directed to a diagnostic method practised on the human or animal body, the search has been carried out and based on the alleged effects of the compostion.

Although claims 27, 30 and 31 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the composition.

Continuation of Box I.2

Present claims 1-11 and 15-19 relate to an extremely large number of possible compounds. In fact, the claims contain so many options for an ovarian carcinoma antigen 0772P that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise.

In view of the description (page 5, line 28-page 6, line 5), an 0772P consensus repeat sequence 'X' as set forth in SEQ ID NO:596 is considered to be a sequence element of 156 amino acids. As a consequence, the search has been limited to an 0772P polypeptide comprising an X repeat 'consisting' of a sequence as defined by the claimed SEQ ID NOs in the application.

Present claim 25 relates to an agent defined by reference to a desirable characteristic or property, namely that it binds to a polypeptide of claim 21.

The claim covers all agents having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such agents. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the agents by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to antibodies binding to a polypeptide of claim 21.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3,7,15,19-32,35, all partially

Invention 1

An 0772P polypeptide having the structure X-Y, wherein X comprises the sequence defined by SEQ ID NO:574 and Y comprises a sequence having at least 80% identity with the sequence of SEQ ID NO:594, a polynucleotide encoding said X repeat defined by SEQ ID NO:542, said polypeptide or polynucleotide being overexpressed in ovarian cancer cells compared with normal tissue, an isolated nucleic acid sequence defined by SEQ ID NO:542, complement thereof, sequence containing at least 20 contiguous residues thereof, sequences that hybridise to said sequence, sequence having at least 75% or 90% identity to said sequence, degenerate variants of said sequence, polypeptides encoded by said sequence, said sequence in an expression vector, a host cell transfected with said expression vector, an isolated antibody binding aforementioned polypeptide, a method of diagnosing cancer using said peptide, a fusion protein comprising said peptide, a method for stimulating or expanding T cells using said polynucleotides or polypeptides and the resulting T cell population, a composition comprising said polynucleotide, polypeptide, antibody, fusion protein, T cell population or antigen presenting cells expressing the polypeptide, a method for stimulating an immune response, a method for treatment of ovarian cancer, a method of determining ovarian cancer in a patient and an antibody against the specific 0772P polypeptide of the invention.

2. Claims: 1-3,7,35, all partially

Inventions 2-20

As for invention 1, but limited to subject-matter relating to polypeptides having an X domain as defined in SEQ ID NOs 575-593, whereby invention 2 is limited to SEQ ID NO:575, invention 3 is limited to SEQ ID NO:576, invention 4 is limited to SEQ IS NO:577, etc..., invention 19 is limited to SEQ ID NO:592 and invention 20 is limited to SEQ ID NO:593

3. Claims: 15 and 19-32, all partially

Invention 21

A polynucleotide encoding an 0772P polypeptide having the structure X-Y, whereby X and Y are encoded by the sequence defined by SEQ ID N0:512 and SEQ ID N0:568, respectively, said polypeptide overexpressed in ovarian cancer cells

compared with normal tissue and an isolated nucleic acid sequence defined by SEQ ID NO:512, complement thereof. sequence containing at least 20 contiguous residues thereof. sequences that hybridise to said sequence, sequence having at least 75% or 90% identity to said sequence, degenerate variants of said sequence, polypeptides encoded by said sequence, said sequence in an expression vector, a host cell transfected with said expression vector, an isolated antibody binding aforementioned polypeptide, a method of diagnosing cancer using said peptide, a fusion protein comprising said peptide, a method for stimulating or expanding T cells using said polynucleotides or polypeptides and the resulting T cell population, a composition comprising said polynucleotide, polypeptide, antibody, fusion protein, T cell population or antigen presenting cells expressing the polypeptide, a method for stimulating an immune response, a method for treatment of ovarian cancer and a method of determining ovarian cancer in a patient.

4. Claims: 15 and 19-32, all partially

Inventions 22-73

As for invention 21, but limited to the subject-matter relating to an X domain encoding polynucleotide as defined in SEQ ID NOs:513-540, 543-546 and 548-567, whereby invention 22 is limited to SEQ ID NO:513, invention 23 is limited to SEQ ID NO:514, invention 24 is limited to SEQ ID NO:540, invention 50 is limited to SEQ ID NO:543, invention 51 is limited to SEQ ID NO:544, invention 52 is limited to SEQ ID NO:545, invention 53 is limited to SEQ ID NO:546, invention 54 is limited to SEQ ID NO:548, invention 55 is limited to SEQ ID NO:549, ..., invention 72 is limited to SEQ ID NO:566 and invention 73 is limited to SEQ ID NO:567

5. Claims: 20-32, all partially

Invention 74

Isolated nucleic acid sequence defined by SEQ ID NO:464, complement thereof, sequence containing at least 20 contiguous residues thereof, sequences that hybridise to said sequence, sequence having at least 75% or 90% identity to said sequence, degenerate variants of said sequence, polypeptides encoded by said sequence, said sequence in an expression vector, a host cell transfected with said expression vector, an isolated antibody binding aforementioned polypeptide, a method of diagnosing cancer using said peptide, a fusion protein comprising said peptide, a method for stimulating or expanding T cells using said polynucleotides or polypeptides and the resulting T cell population, a composition comprising said

polynucleotide, polypeptide, antibody, fusion protein, T cell population or antigen presenting cells expressing the polypeptide, a method for stimulating an immune response, a method for treatment of ovarian cancer and a method of determining ovarian cancer in a patient.

6. Claims: 20-32, all partially

Inventions 75-91

As for invention 74, but limited to the subject-matter relating to an nucleic acid sequence as defined in SEQ ID NOs:465-477, 541, 547, 568 and 569, wherein invention 75 is limited to SEQ ID NO:465, invention 76 is limited to SEQ ID NO:466, invention 77 is limited to SEQ ID NO:467, invention 78 is limited to SEQ ID NO:468, invention 79 is limited to SEQ ID NO:469, invention 80 is limited to SEQ ID NO:470, invention 81 is limited to SEQ ID NO:471, invention 82 is limited to SEQ ID NO:472, invention 83 is limited to SEQ ID NO:473, invention 84 is limited to SEQ ID NO:474, invention 85 is limited to SEQ ID NO:475, invention 86 is limited to SEQ ID NO:476, invention 87 is limited to SEQ ID NO:477, invention 88 is limited to SEQ ID NO:541, invention 89 is limited to SEQ ID NO:568, invention 91 is limited to SEQ ID NO:569

7. Claims: 33, partially

Invention 92

An 0772P polypeptide comprising at least an antibody epitope sequence set forth in SEQ ID NO:490

8. Claims: 33, partially

Inventions 93-113

As for invention 92, but limited to the subject-matter relating to an antibody epitope as defined in SEQ ID NO:491-511, wherein invention 93 is limited to SEQ ID NO:491, invention 94 is limited to SEQ ID NO:492, ..., invention 113 is limited to SEQ ID NO:511

9. Claims: 34, partially

Invention 114

An O8E polypeptide comprising at least an antibody epitope sequence set forth in SEQ ID NO:394

10. Claims: 34, partially

Inventions 115-135

As for invention 114, but limited to the subject-matter relating to an antibody epitope as defined in SEQ ID NOs:395-415, wherein invention 115 is limited to SEQ ID NO:395, invention 116 is limited to SEQ ID NO:396, ..., invention 135 is limited to SEQ ID NO:415

page 4 of 4

INTERNATIONAL SEARCH REPORT

Information on patent family members

tonal Application No
PCT/US 01/22635

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